

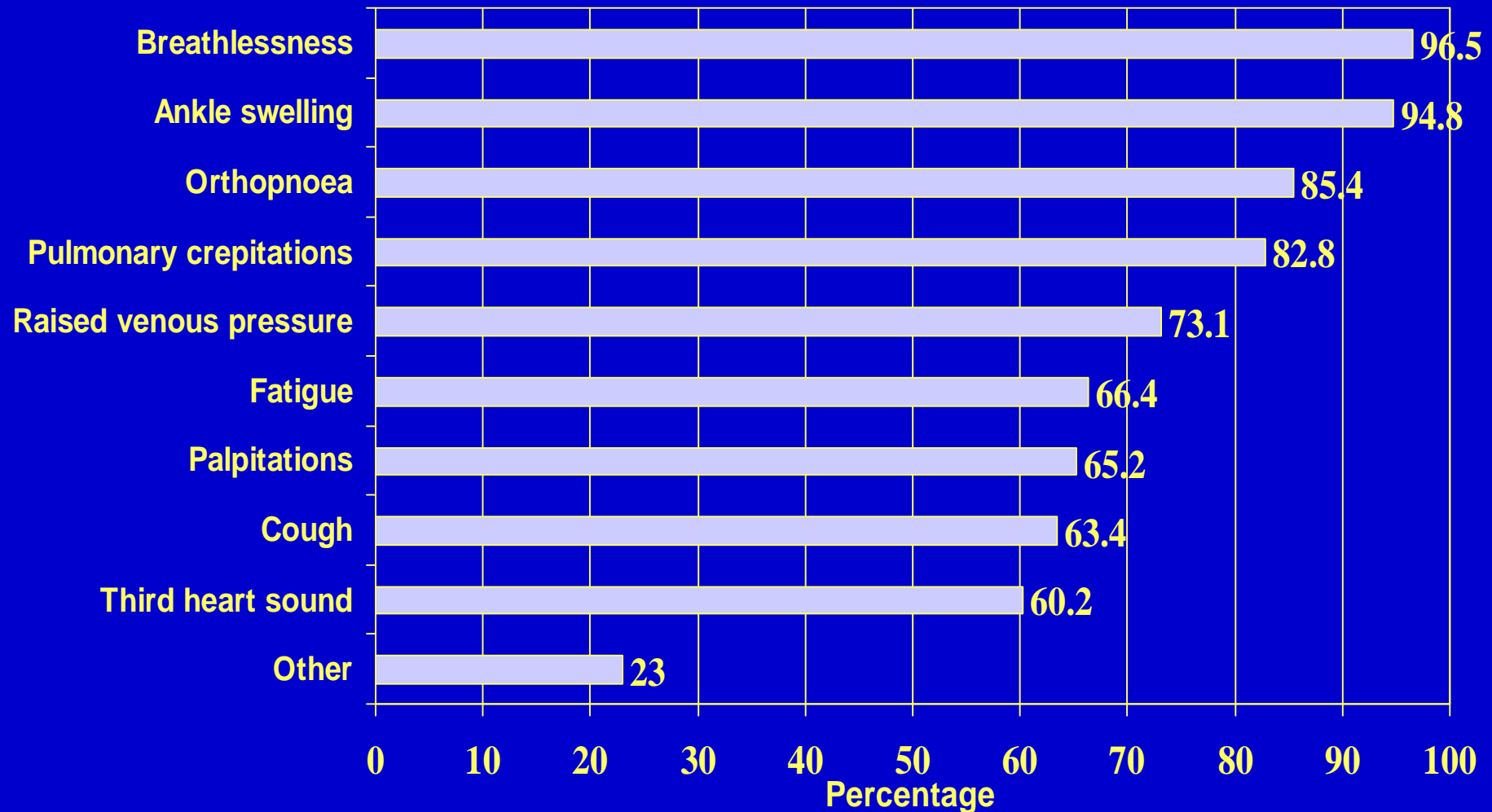
Heart Failure Management

JFD 2003

The Growing Burden of Heart Failure

- ◆ Prevalence of heart failure is rising in industrialized countries
 - Due to aging populations, hypertension, and improved survival in coronary artery disease (post-MI)
 - Overall rate estimated is 3–20 per 1000
 - In those older than 65 years, 30–130 per 1000
- ◆ 1-year heart failure mortality rates are 35% to 45% in newly diagnosed cases
- ◆ Heart failure is the single most frequent and expensive cause of hospitalization in those older than age 65

Common Signs / Symptoms Leading GPs to Suspect Heart failure



Framingham criteria for a clinical diagnosis of heart failure

2 major or 1 major and 2 minor criteria required,

Major

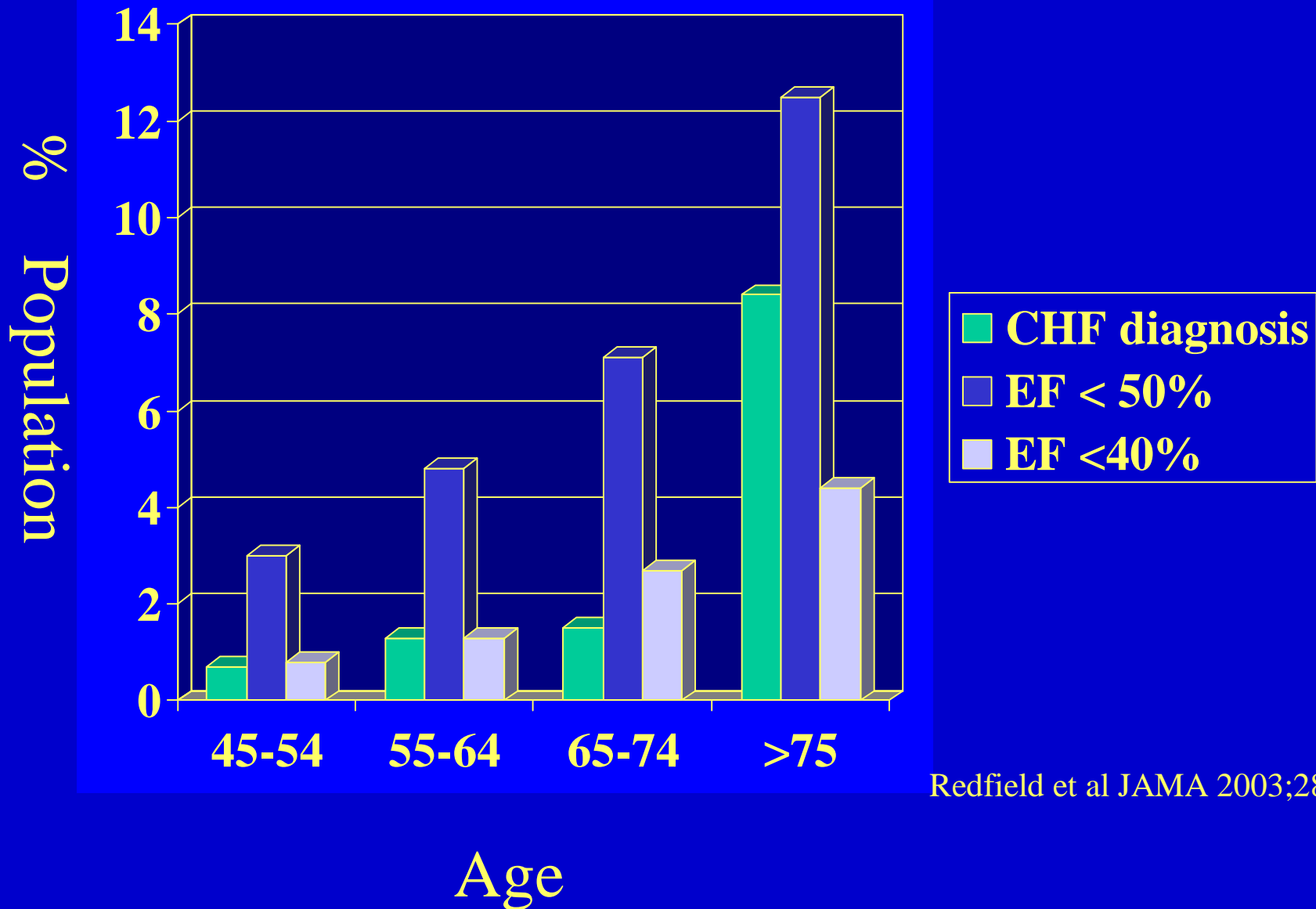
- PND
- Othopnoea
- Elevated JVP
- Pulmonary rales
- 3rd heart sound
- Cardiomegaly on CXR
- Pulmonary oedema on CXR

Minor

- Peripheral oedema
- Night cough
- Dyspnoea on exertion
- Hepatomegaly
- Pleural effusion
- Heart rate $>120/\text{min}$
- Weight loss $\geq 4.5\text{kg}$ in 5 days*

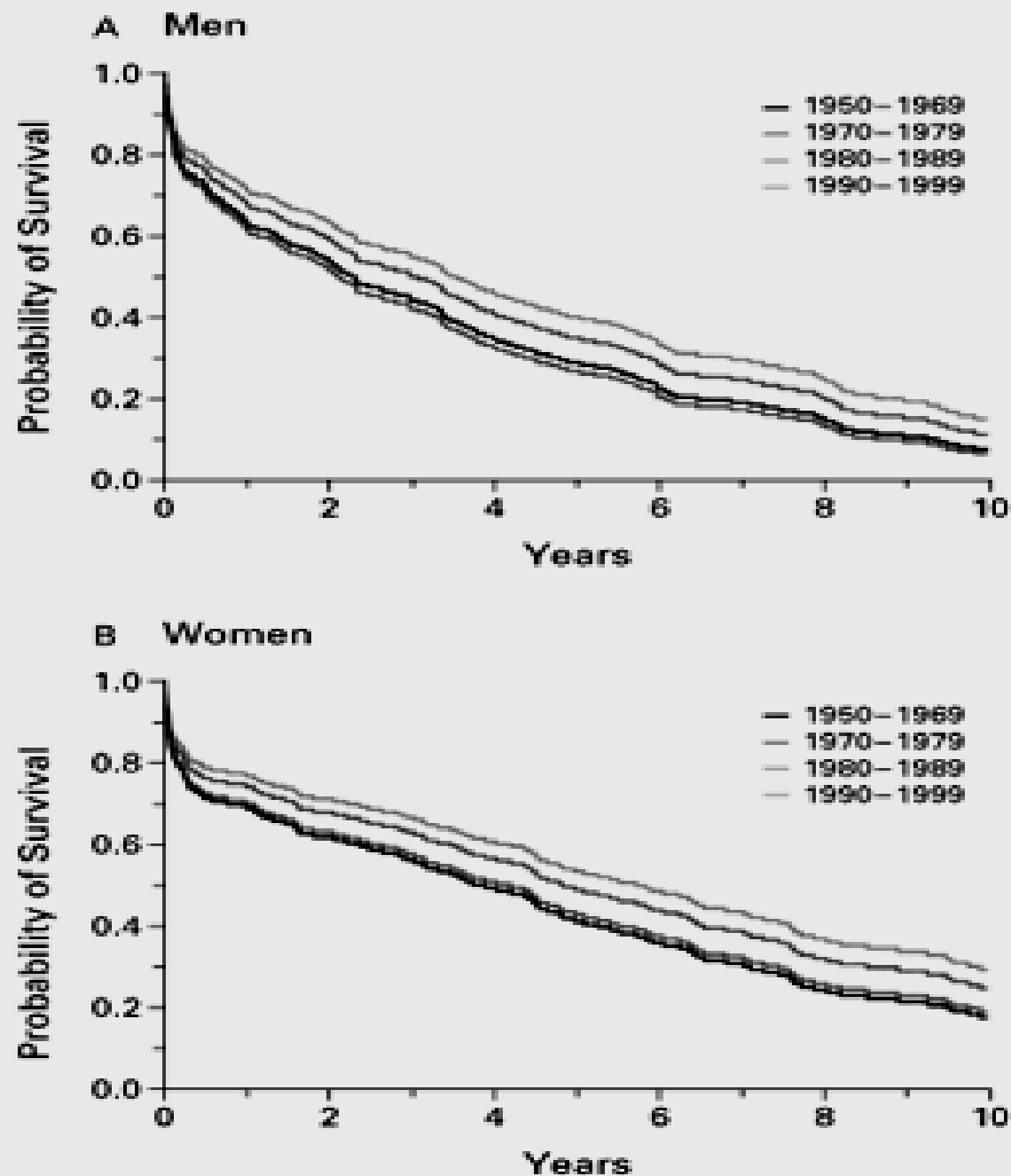
* Weight loss $\geq 5\text{kg}$ in 5 days considered a major criterion if in response to diuretic therapy

Community incidence of Heart Failure



Trends in heart failure survival

NEJM 2002;347:1397 1402



Symptomatic Screening (heart failure symptoms) – Primary Care

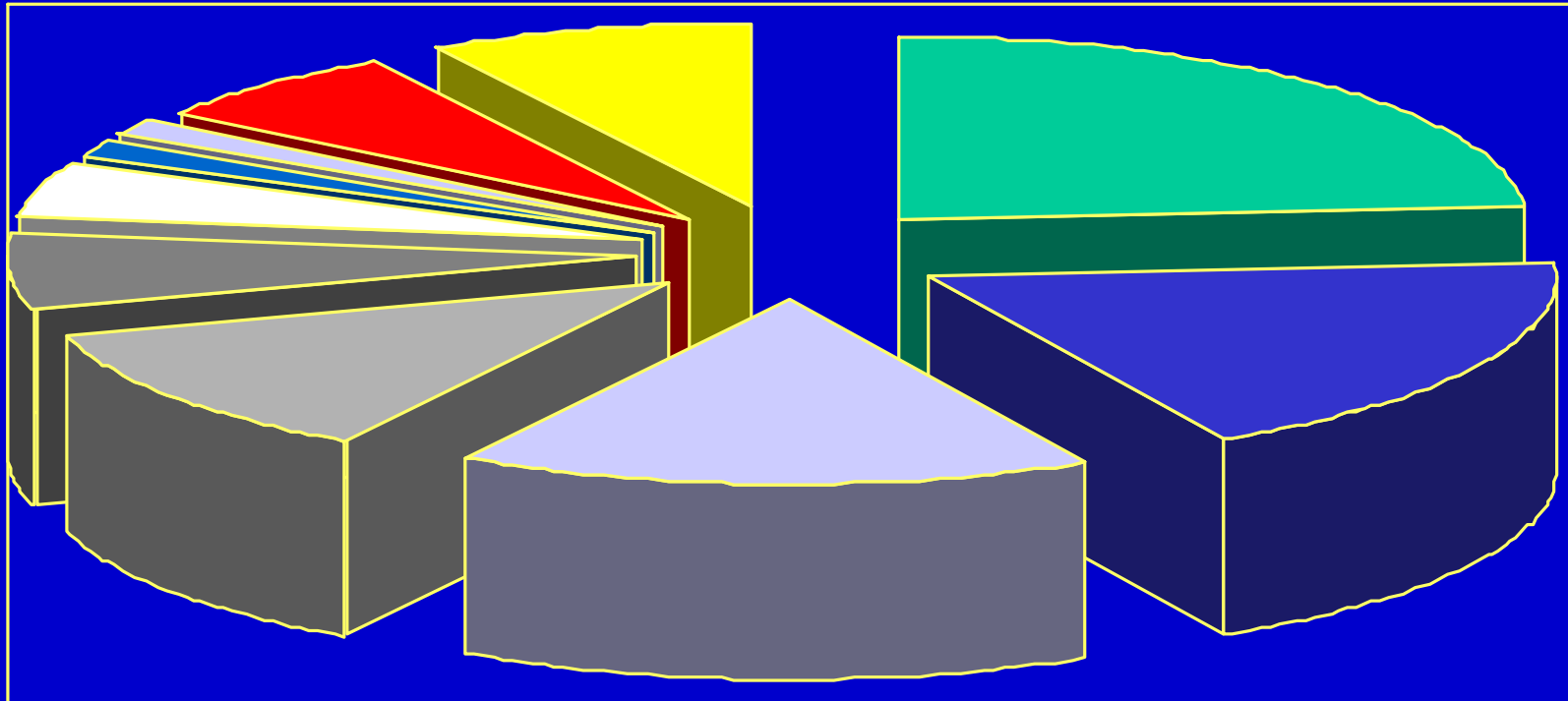
Cowie et al Lancet 1997; 350: 1347-51

- Of patients referred

- 29% met criteria for heart failure*
- 22% chronic obstructive pulmonary disease
- 20% obesity
- 14% angina*
- 8% Venous insufficiency
- 6% arrhythmias*
- 6% anxiety
- 2% pulmonary fibrosis*
- 2% malignant disorders*
- 10% others

*Needing referral = 53%

Distribution of diagnosis – Hillingdon heart study



■ LVF

■ Angina

■ Pulmonary fibrosis

■ Others

■ COPD

■ Venous insufficiency

■ Malignancy

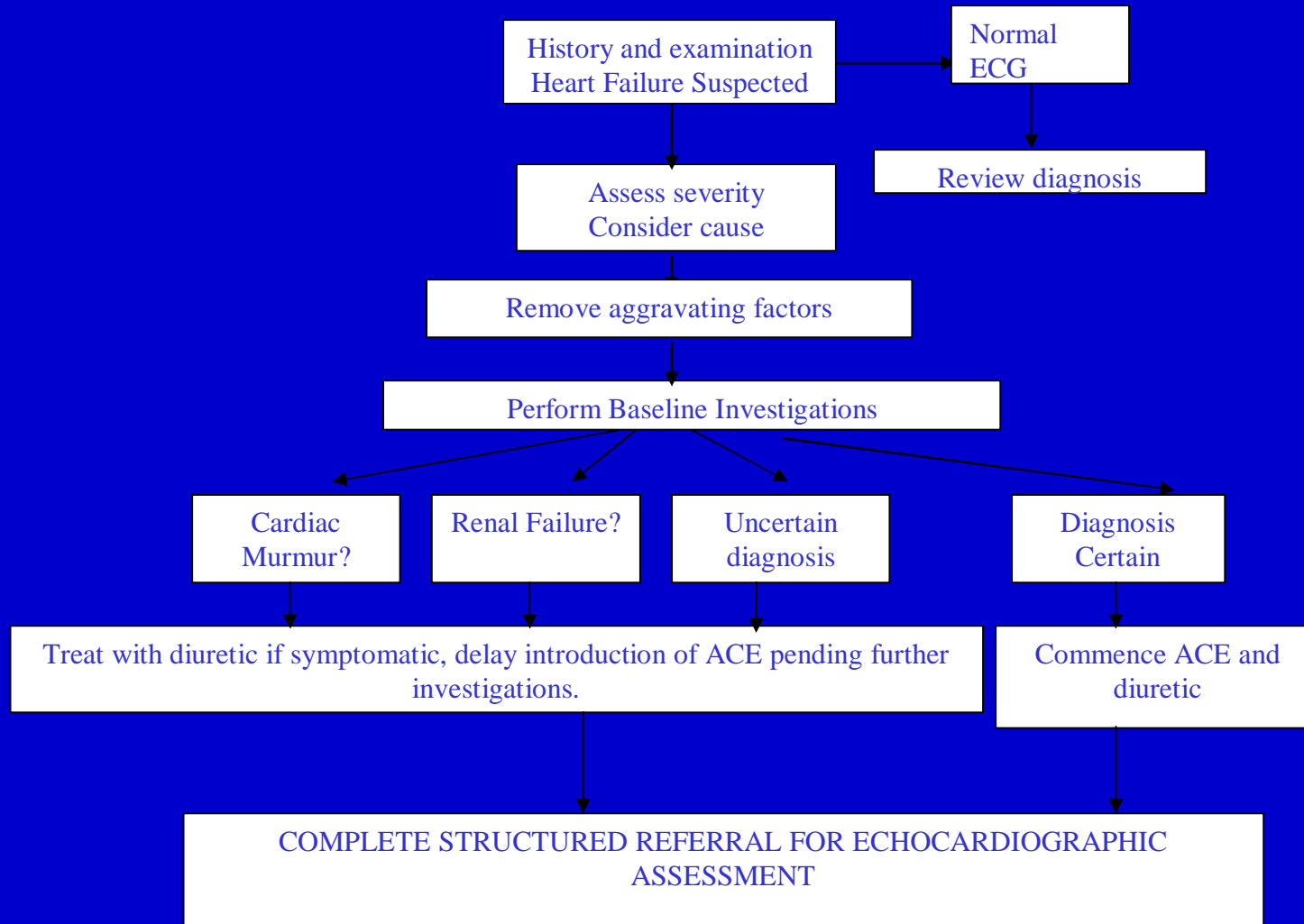
■ Obesity

■ Arrhythmias

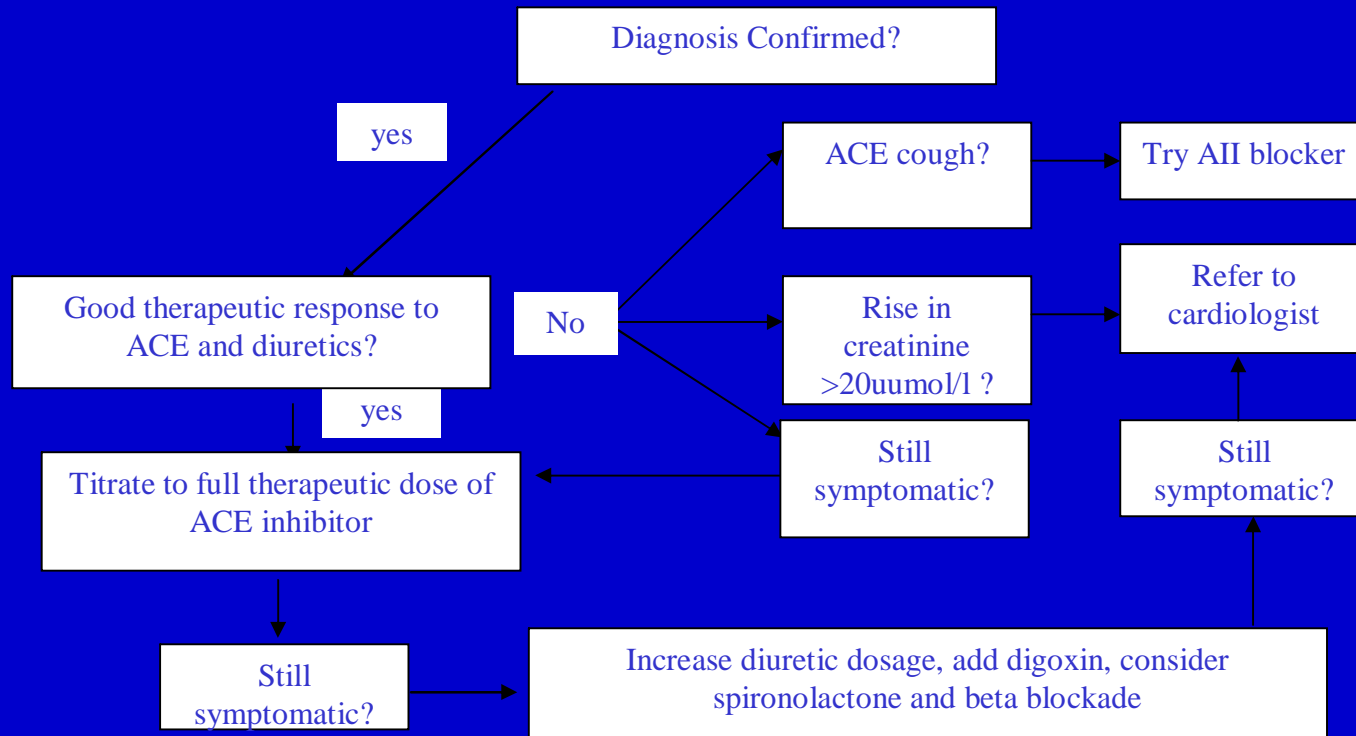
■ Anxiety

Heart failure management

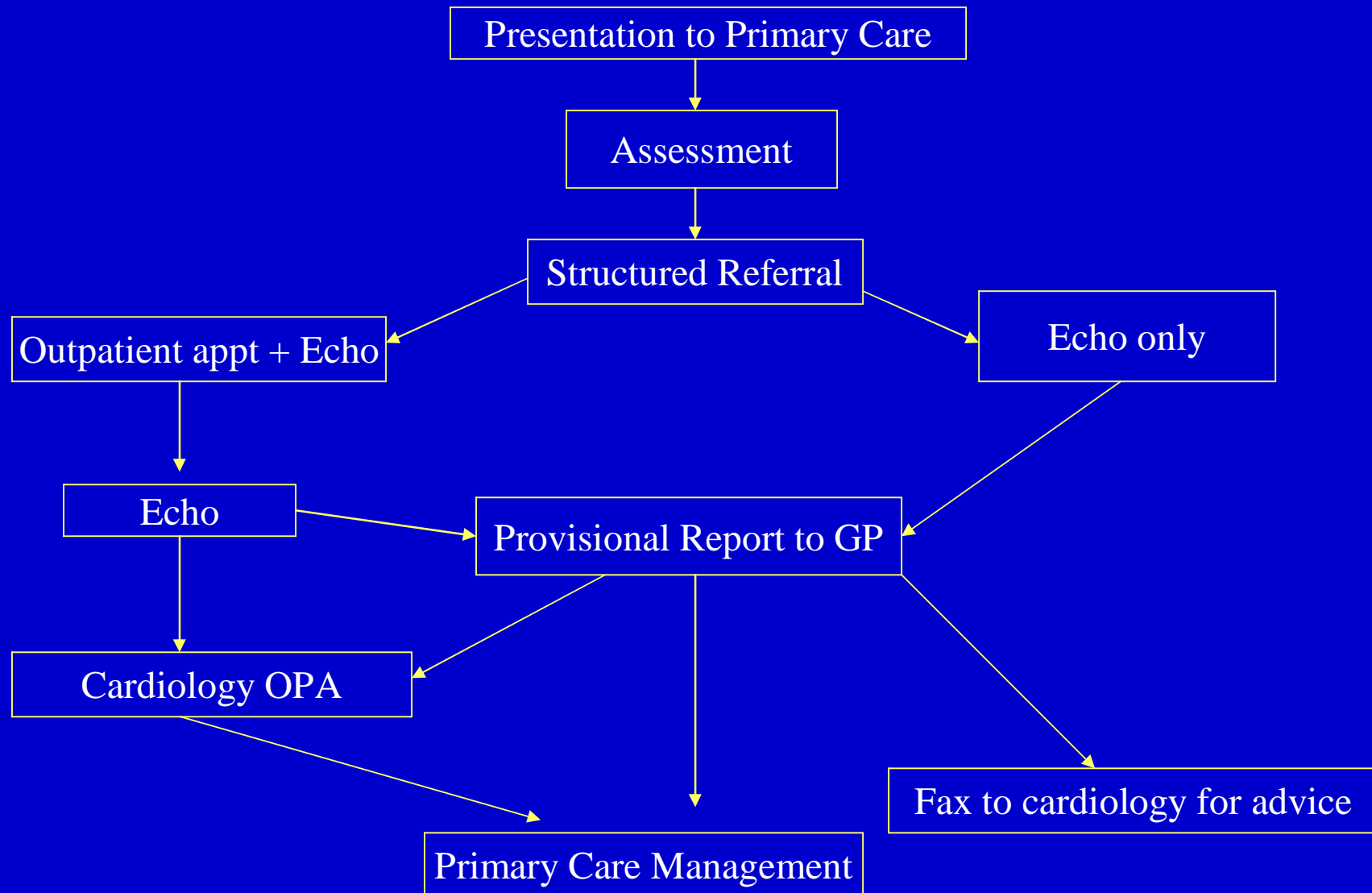
STAGE ONE – INITIAL INVESTIGATION AND ASSESSMENT



STAGE TWO – SUBSEQUENT MANAGEMENT



Heart Failure Echo Clinic



Case 1

- 75 yr old man
- 7 yr history of dyspnoea on exertion
- 3/12 history of ankle oedema
- 3 pillow orthopnoea
- Smoker of 30/day for 40 years
- P 70 BP 130/80 JVP + 6
- Chest hyperinflated
- ECG normal

Screening (history of heart disease) – Community

Nielsen et al BMJ 2000; 320: 220

- Risk of heart failure with ECG not showing; ST depression, Left bundle branch block or Q waves <2%.

Case 2

- 36 yr old man
- 1/12 increasing dyspnoea, ankle oedema and palpitations
- Non smoker. Alcohol 1 bottle of wine per day
- P120 AF BP 130/80 JVP 2 HS normal
- Chest: basal crepitations
- ECG: AF
- CXR: cardiomegaly

Case 2

- Alcoholic cardiomyopathy
 - Early presentation with AF
 - Potentially reversible
 - Complete abstinence
- Tachycardia induced cardiomyopathy
 - Fast AF, atrial flutter
 - Reversible with rhythm control

Case 3

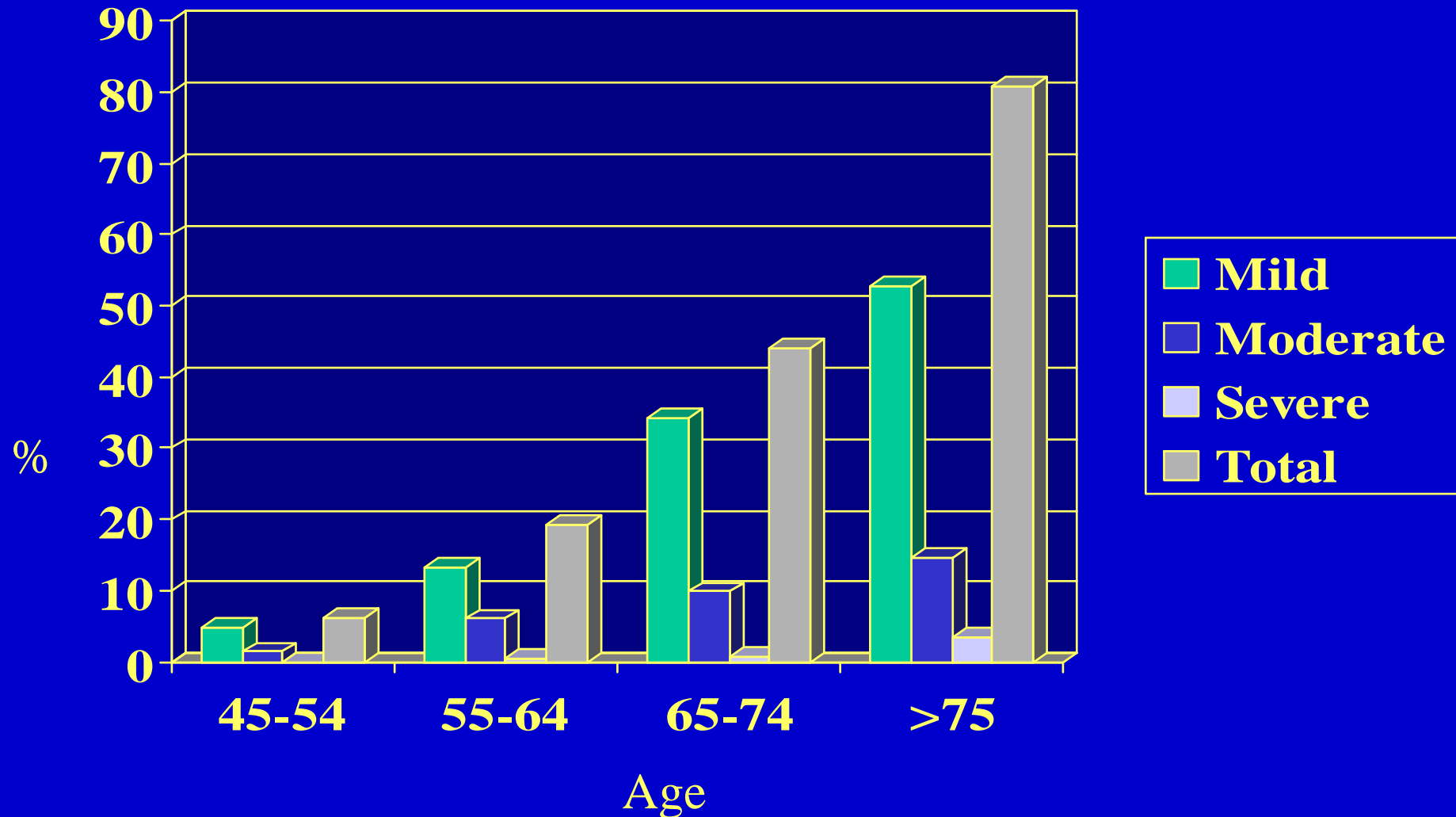
- 57 yr old man
- 10 yr history of hypertension on thiazide
- 6/12 history of dyspnoea
- Smoker 20/day. NIDDM
- P 80 SR BP 200/120 JVP 2 HS soft systolic murmur
- Chest clear
- ECG lateral T wave flattening.
- U+E Na 135 K3.0 Ur 9 Cr 150

Case 3

- Consider
 - Diastolic dysfunction
 - Renal artery stenosis
 - Coronary artery disease
- ACE inhibition?

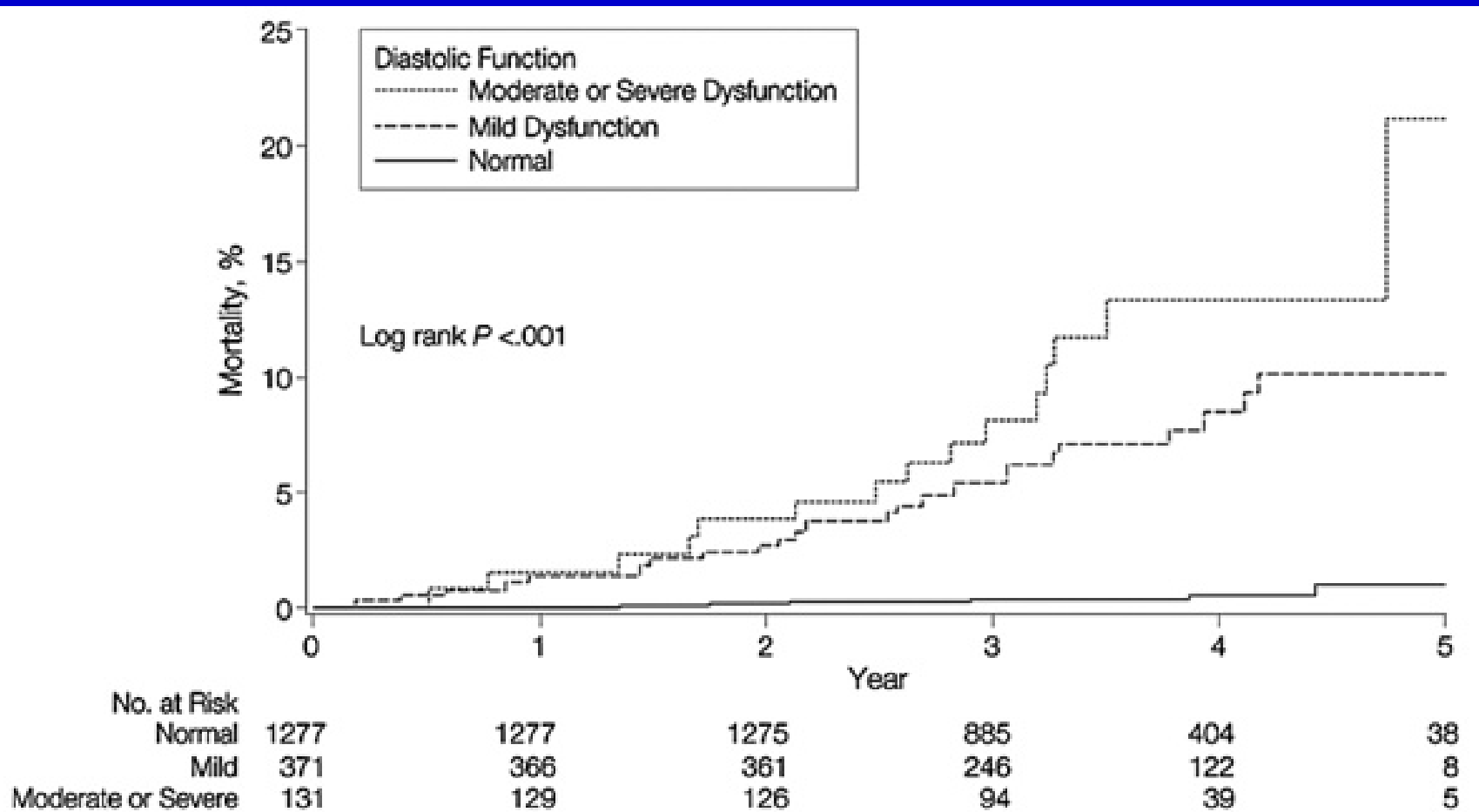
Diastolic dysfunction and age

Redfield et al JAMA 2003;289:194

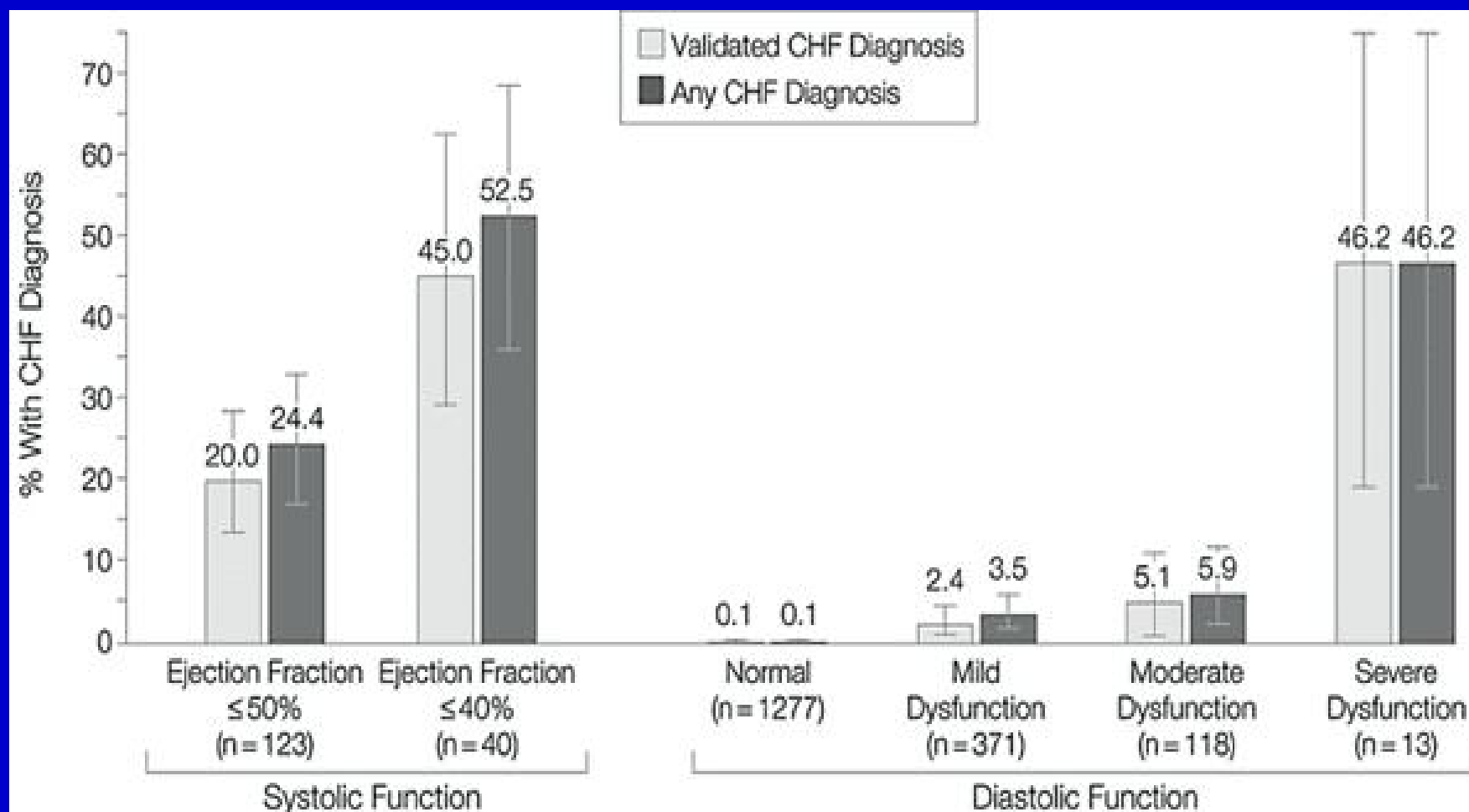


Survival and diastolic dysfunction

Redfield et al JAMA 2003;289:194



Relationship between congestive cardiac failure diagnosis and ventricular dysfunction



Systolic vs diastolic dysfunction – clinically important different disorders?

- High risk ie Age ≥ 65 and hypertension or coronary disease approximately doubles the risk of systolic and diastolic dysfunction
- Isolated diastolic dysfunction occurs in only 5.6% of patients with moderate or severe diastolic dysfunction.

Case 4

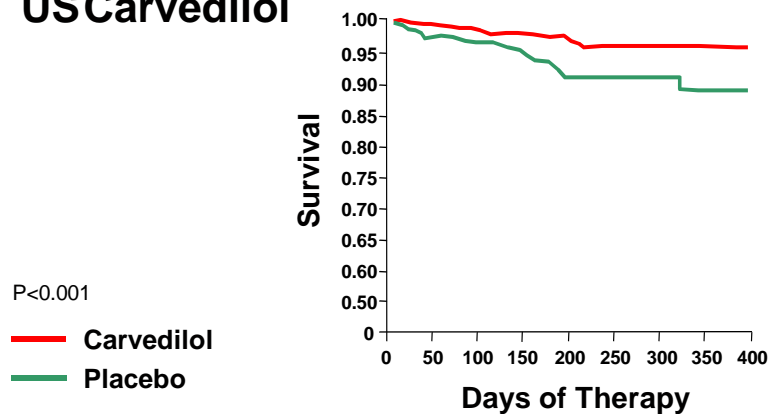
- 79yr old woman
- 4/12 history of dyspnoea on exertion (100yds)
- 10yr history of hypertension on atenolol 100mg daily
- 5 yr history of angina
- P60 BP 160/100 JVP 6 LV+ Chest few basal crackles
- ECG – LVH CXR gross cardiomegaly /pulmonary venous congestion

Case 4

- Continue or stop beta blocker?
- Change beta blocker?
- ACE or diuretic first?

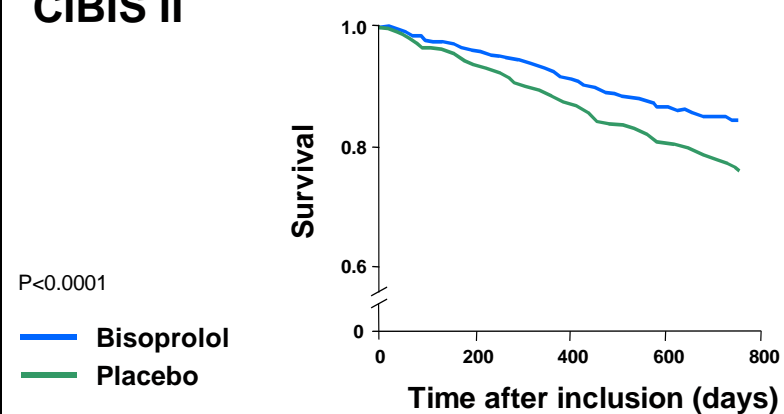
THE BIG BETA-BLOCKER TRIALS

US Carvedilol



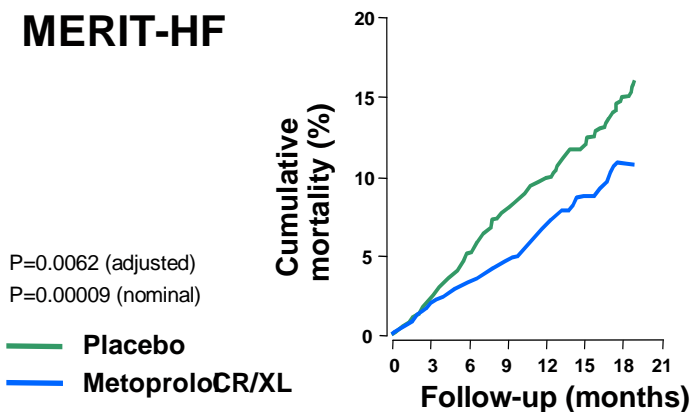
Packer M et al. for the US Carvedilol Heart Failure Study Group. Effects of carvedilol on morbidity and mortality in chronic heart failure. *N Engl J Med* 1996;334:1349-1355

CIBIS II



Dargie HJ, Lechat P. The cardiac insufficiency bisoprolol study II (CIBIS II): A randomised trial. *Lancet* 1999; 353:9-13

MERIT-HF



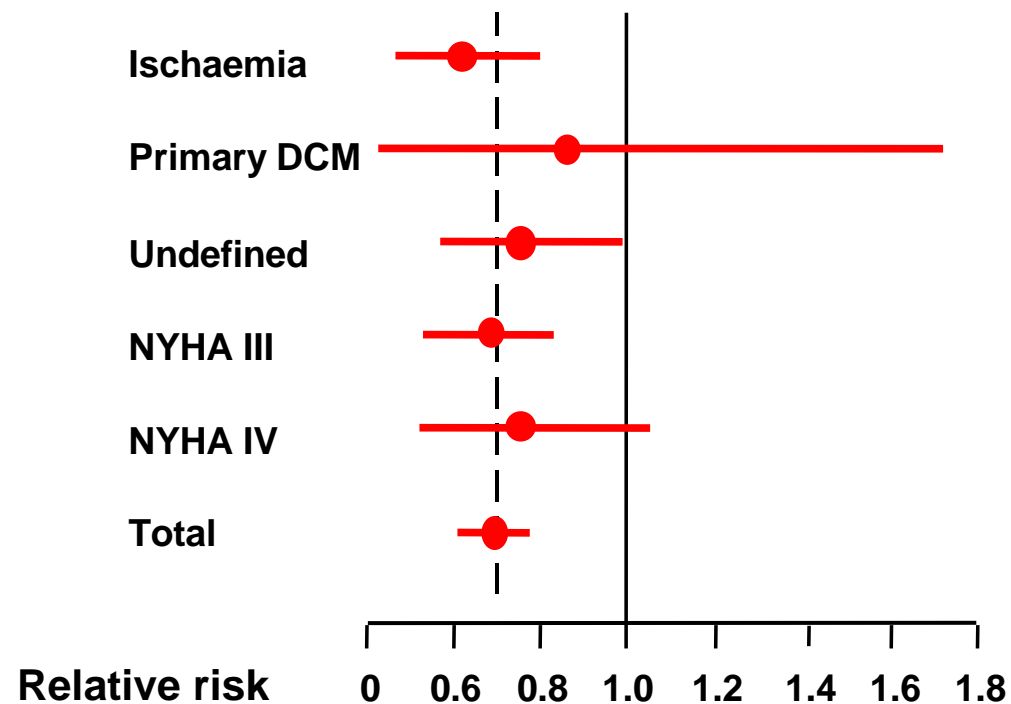
Anonymous: Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *MERIT-HF Study Group* 1999;353:2001-2007

Meta- Analysis

Trial	n	OR (95% CI)
Metaanalysis	3141	0.69 (0.54-0.89)
24 trials including MDC, CIBIS I, ANZ and US Carvedilol		
CIBIS II	2647	0.66 (0.54-0.81)
MERIT-HF	3991	0.66 (0.53-0.81)

Cleland JGF, McGowan J, Clark A. The evidence for beta-blockers in heart failure. *Br Med J* 1999;318:824-825

CIBISII - MORTALITY BENEFIT IN SUB GROUPS

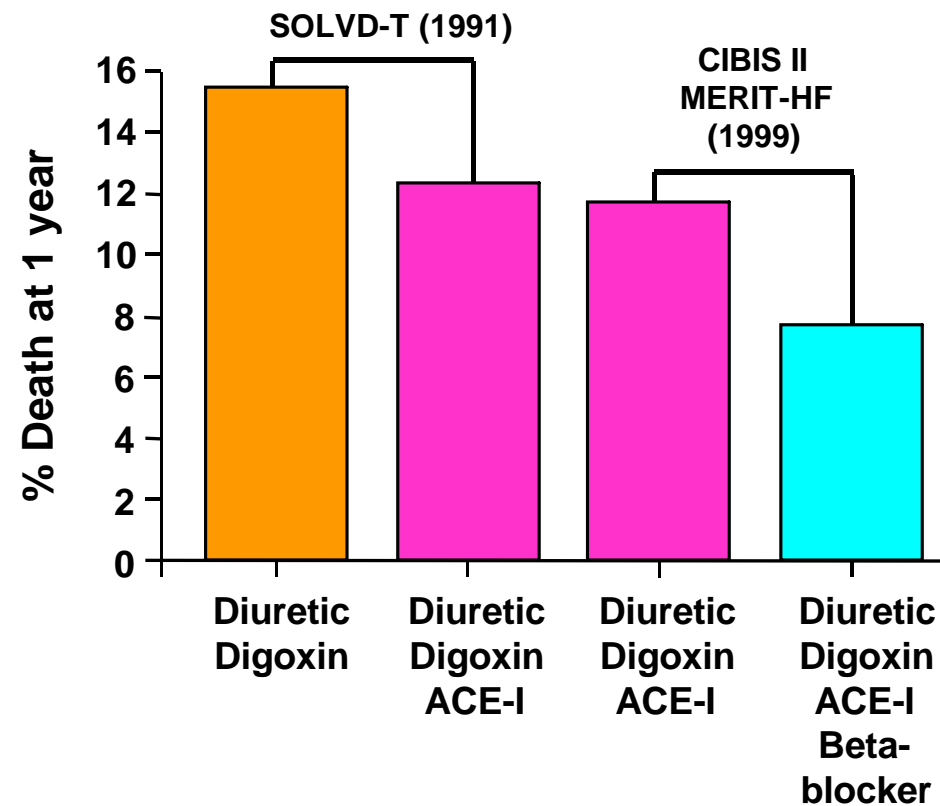


Relative risk of treatment effect on mortality by aetiology and functional class at baseline. Horizontal bars represent 95% CI.

TREATMENT DOSING IN LARGE BETA-BLOCKER MORTALITY ANALYSIS

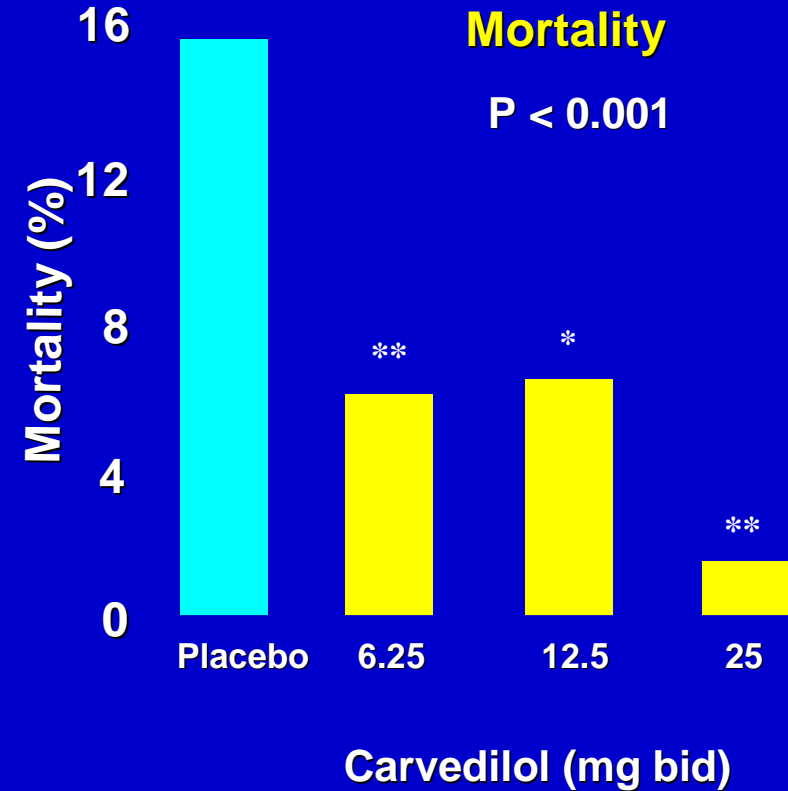
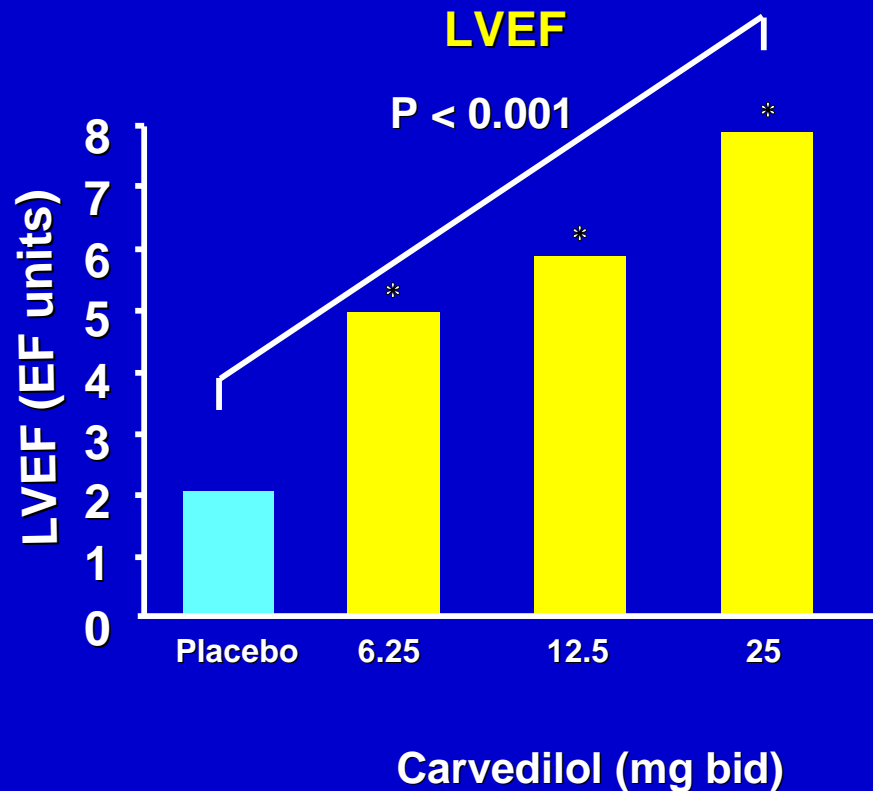
	USCP	CIBISI	MERIT-HF
Proportion of patients reaching target dose in β blocker group (%)	80	43	64
Proportion of patients reaching half or more of target dose (%)	-	67	87
Mean dose in β blocker group (mg)	45	6.6	159
Proportion stopping treatment early (%)			
Placebo	18	15	15.3
β blocker	11	15	13.9

MORTALITY BENEFIT OF BETA-BLOCKERS AND ACE INHIBITORS IN CHF TRIALS



Carvedilol Dose-response Trial (MOCHA)

Effect on LVEF and mortality

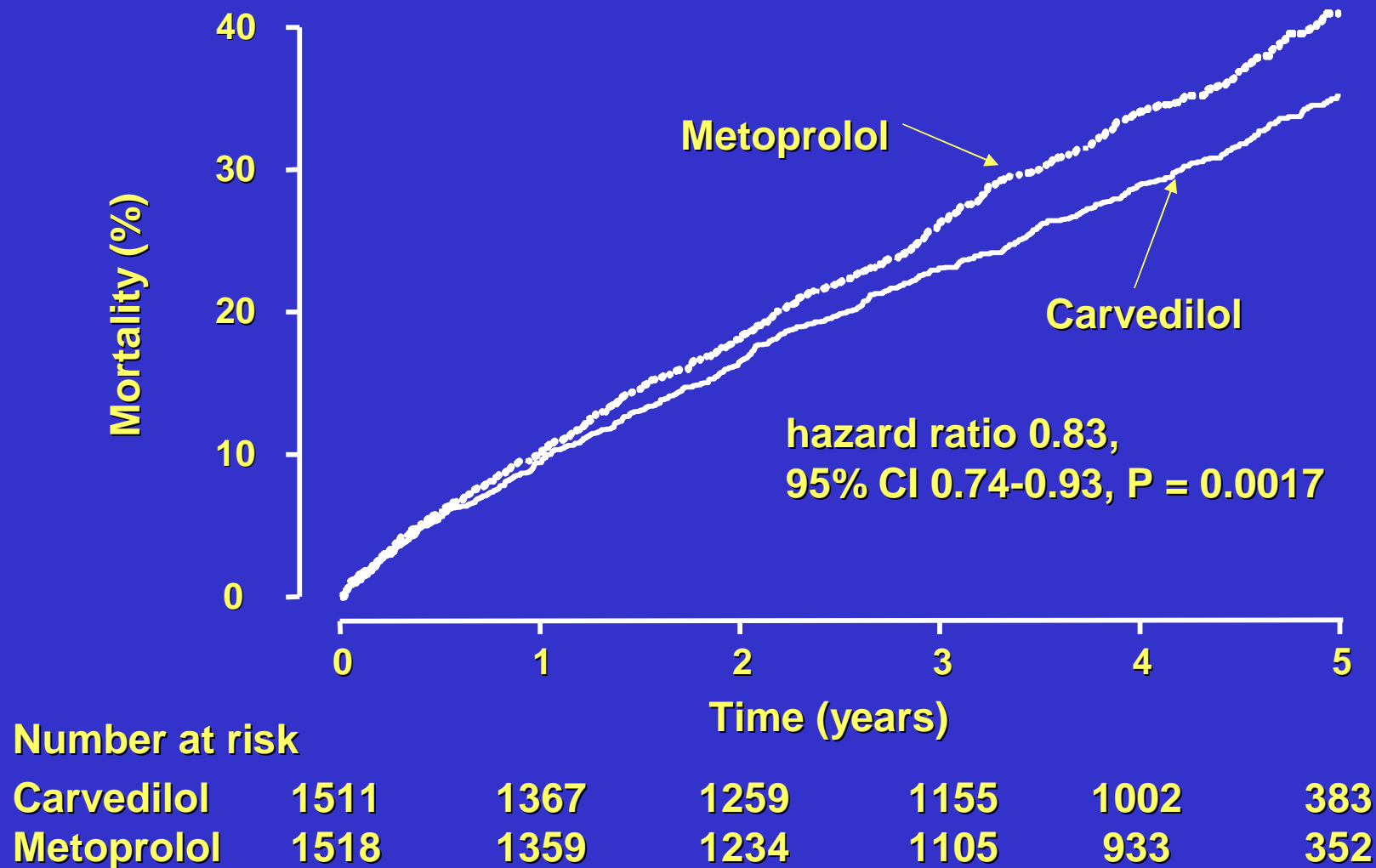


Placebo (n=84); carvedilol (n=261)

Patients receiving diuretics, ACE inhibitors \pm digoxin; follow-up 6 months

Bristow et al. 1996

Primary endpoint of mortality – COMET STUDY



Summary and conclusion

- COMET is the longest and largest study in CHF
- First head-to-head mortality study comparing two beta-blocking agents in CHF
- Carvedilol saved significantly more lives than metoprolol (by 17%, $P = 0.0017$)
- Carvedilol compared to metoprolol reduced annual mortality from 10.0% to 8.3% and prolonged median survival by 1.4 years
- Carvedilol is the preferred beta-blocker for the treatment of chronic heart failure

Case 5

- 68 yr old man
- Long standing LVF echo EF 30%
- On Lisinopril 30 mg daily, Frusemide 80mg bd, Spironolactone 50mg daily, digoxin 0.25mg daily.
- Presents after 6 days diarrhoea and vomiting
- P50 BP 100/60 JVP not visible HS normal Chest clear
- Na 125, K 5.0, Ur 18, Cr 190 (previously normal)

Case 5

- To admit or not to admit?

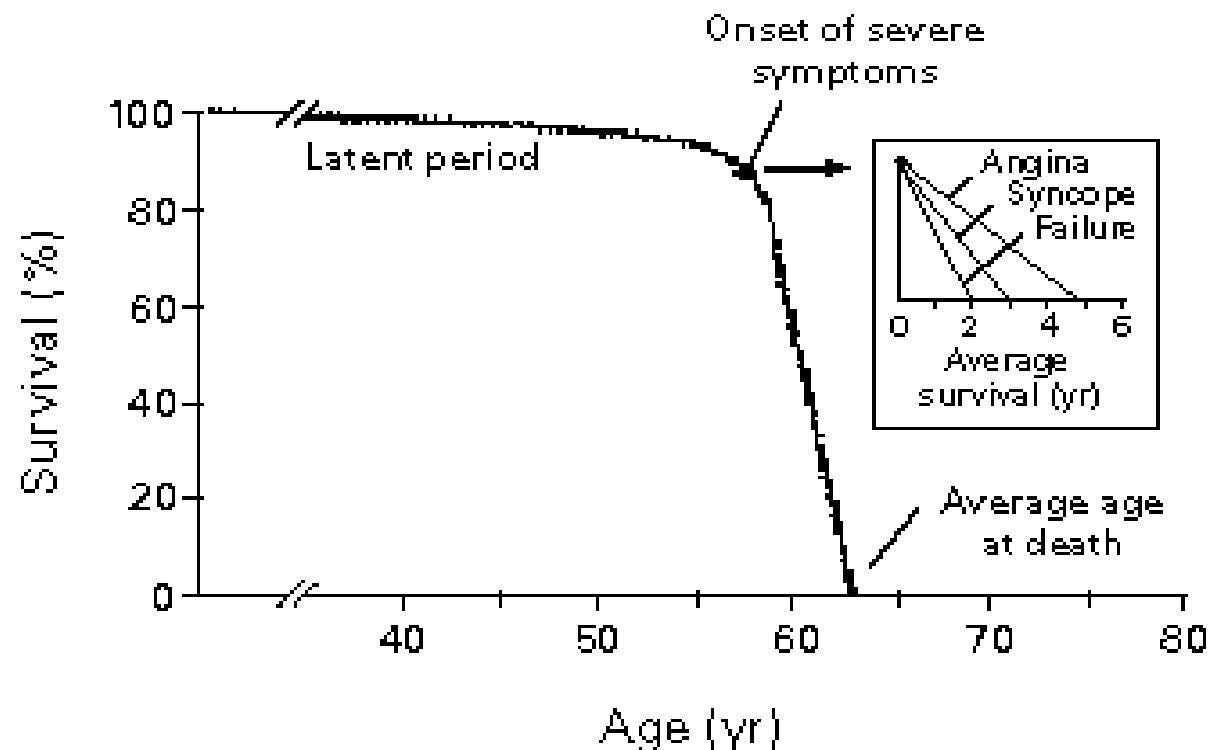
Case 6

- 80 yr old man
- 1 yr history of dyspnoea and chest pain
- Orthopnoea and PND, leg oedema
- Non smoker. Previously hypertensive
- On Lisinopril 10 mg o od
- P90 BP 90/60 JVP +9 LV+ HS barely audible systolic murmur. Chest creps to midzones
- Electrolytes Ur 11.0 Creatinine 100
- ECG gross LVH CXR cardiomegaly and pulmonary oedema

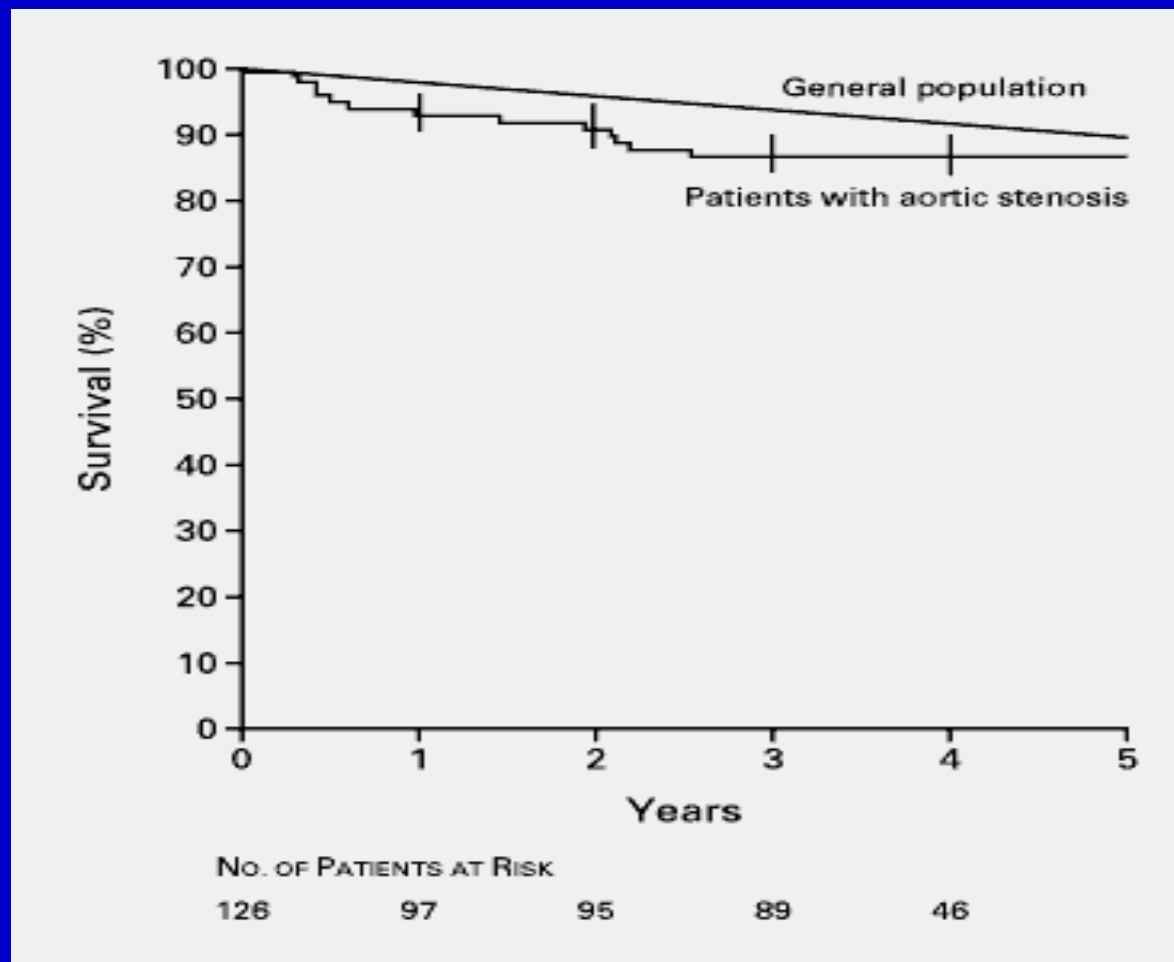
Case 6

- What should you worry about?
- Would you continue the ACE?

SYMPTOMS AND OUTCOME IN AORTIC STENOSIS



AORTIC STENOSIS – ASYMPTOMATIC PATIENTS



Kaplan–Meier Analysis of Overall Survival among 126 Patients with Asymptomatic but Severe Aortic Stenosis, as Compared with Age- and Sex-Matched Persons in the General Population.

Case 7

- 65 yr old insulin dependent diabetic
- Previous anterior MI
- Known chronic renal impairment
- Presents with dyspnoea on exertion over 1 week
- On Frusemide 80mg daily, intolerant of ACE inhibitors (progressive renal impairment), alpha calcidol, titralac, amlodipine 10 mg daily, atenolol 100 mg daily
- P45 AF BP 170/100 JVP +8 LV+ HS normal
- Chest creps to midzones. Pitting oedema to knees
- Na 140 K 4.5 Cr 350 Ur 25 Hb 9.0 WCC 4.5 Plts 200. ECG anterior q wave formation

Case 7

- What next?

Hydralazine and Nitrates

- V-Heft study
 - Hydralazine (25-50 mg tds) and isosorbide dinitrate
 - Pre-ACE inhibitors
 - Useful in renal failure patients

Case 7b

- 65 yr old man
- History of hypertension
- Has chest x ray showing cardiomegaly following chest infection
- ECG minor T wave inversion
- ECHO ejection fraction 40%
- Asymptomatic
- What do you do?

Does asymptomatic heart failure matter?

- Annual CHF rate = 4.9 – 20%
- Annual mortality = 5.1 – 10.5%
- Data from SAVE and SOLVD
- Does the HOPE data include a proportion of these patients?

A disturbing diagnostic problem

If 50% of left ventricular function is asymptomatic then in a patient who presents with breathlessness in a significant proportion the demonstration of LV dysfunction or a raised BNP may not be the cause.

Case 8

- 90 yr old woman
- Known LVF and angina. Presents with falls.
- Drugs
 - Frusemide 120 mg mane
 - Lisinopril 10mg mane
 - Digoxin 250ug mane
 - Warfarin
 - ISMN 20 mg BD

Case 8 continued

- P 55 AF BP 160/80 lying JVP 0 HS long standing pan systolic murmur. Chest clear
- ECG AF only

Case 8

- What do you stop first?
- Is the murmur significant?

Digoxin

- DIG Study
 - Digoxin for heart failure patients in sinus rhythm
 - No effect on mortality
 - Reduced hospital admissions
 - NNT 13
 - 4% more suspected toxicity
 - Small increase in arrhythmias (NS)

Digoxin

- Useful drug in severe heart failure
- Smaller doses needed than for rate control of AF
- Monitoring of digoxin levels only needed if:
 - Renal dysfunction
 - Symptoms of toxicity

Using digoxin in heart failure

- The beneficial effects of digoxin are independent of serum digoxin concentration
 - Kirkwood et al J Am Coll Cardiol 2002; 39:946-53

Case 9

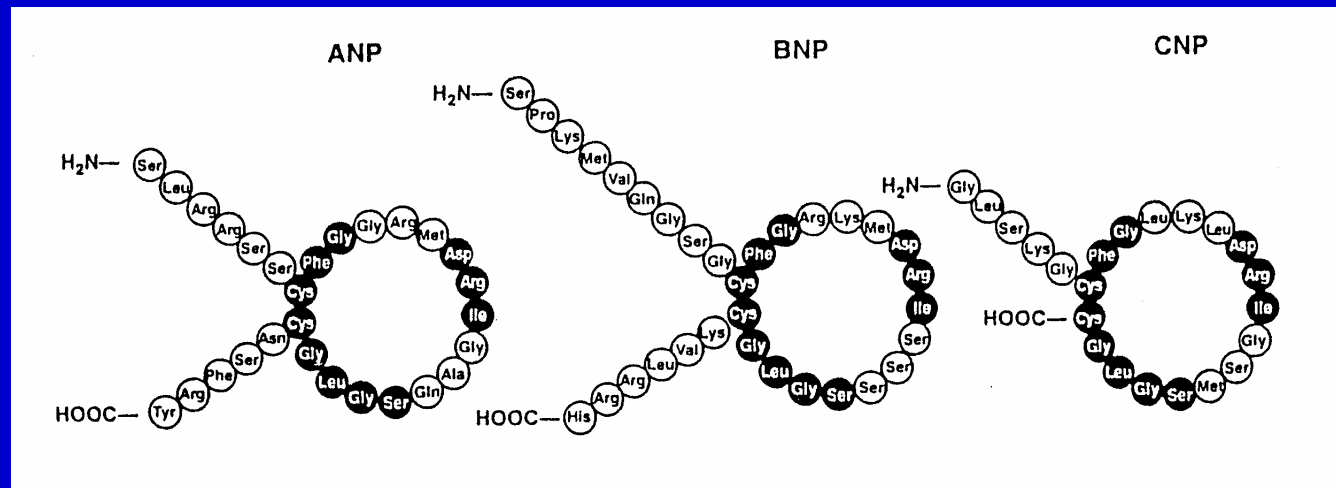
- 70 yr old man
- Previous MI and peripheral vascular disease
- 7/12 increasing breathlessness - exercise tolerance 20 yds. Orth 4 pillows.
- On atenolol 25 mg daily, Aspirin 75 mg daily, voltarol 75mg bd
- Smoker 30/day. Alcohol 25 unit per week
- P70 BP 150/100 JVP +5 LV+ HS soft ejection systolic murmur. Chest bibasal crepitations
- ECG inferior Q waves. CXR normal
- Na 135 K 4.0 Cr 125 Ur 8.5

Case 10

- 25 yr old athlete
- Father dilated cardiomyopathy
- Internet enthusiast
- Examination normal
- ECG normal
- CXR mild cardiomegaly

Natriuretic Peptide Structures

- Structurally similar :a common 17 AA ring structure with 11 identical AA. This ring structure is essential for receptor binding (Guanylate cyclase linked receptor)



Distinct gene expression. CNP has a very low concentration in plasma, not increased in CHF.

The Circulating Cardiac Hormones

ANP

- ANP: Atrial Natriuretic Peptide (A-type NP)
- 28 AA and 5- 9 min half-life
- Major origin: cardiac atrial and ventricular tissue
- Increased in CHF
- Stimulus: Atrial wall tension

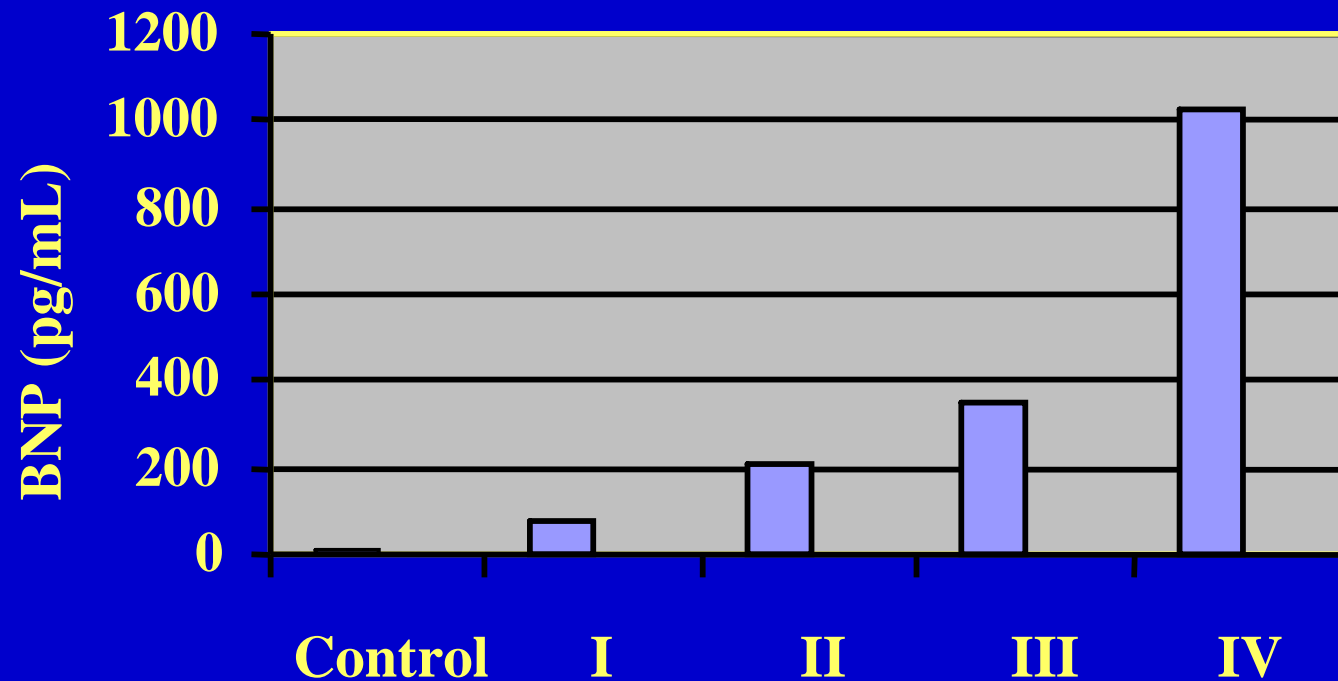
BNP

- BNP: B- type Natriuretic Peptide
- 32 AA and 22 min half-life
- Major origin: ventricles
- Strongly increased in CHF
- Stimulus: ventricular stretch and ventricular wall tension

B-Type Natriuretic Peptide (BNP)

- Found only in the cardiac ventricles
- Released in response to stretch and increased volume in the ventricle
- BNP levels correlate with:
 - **NYHA classification**
 - **Left ventricular end-diastolic pressure**
 - **Prognosis**

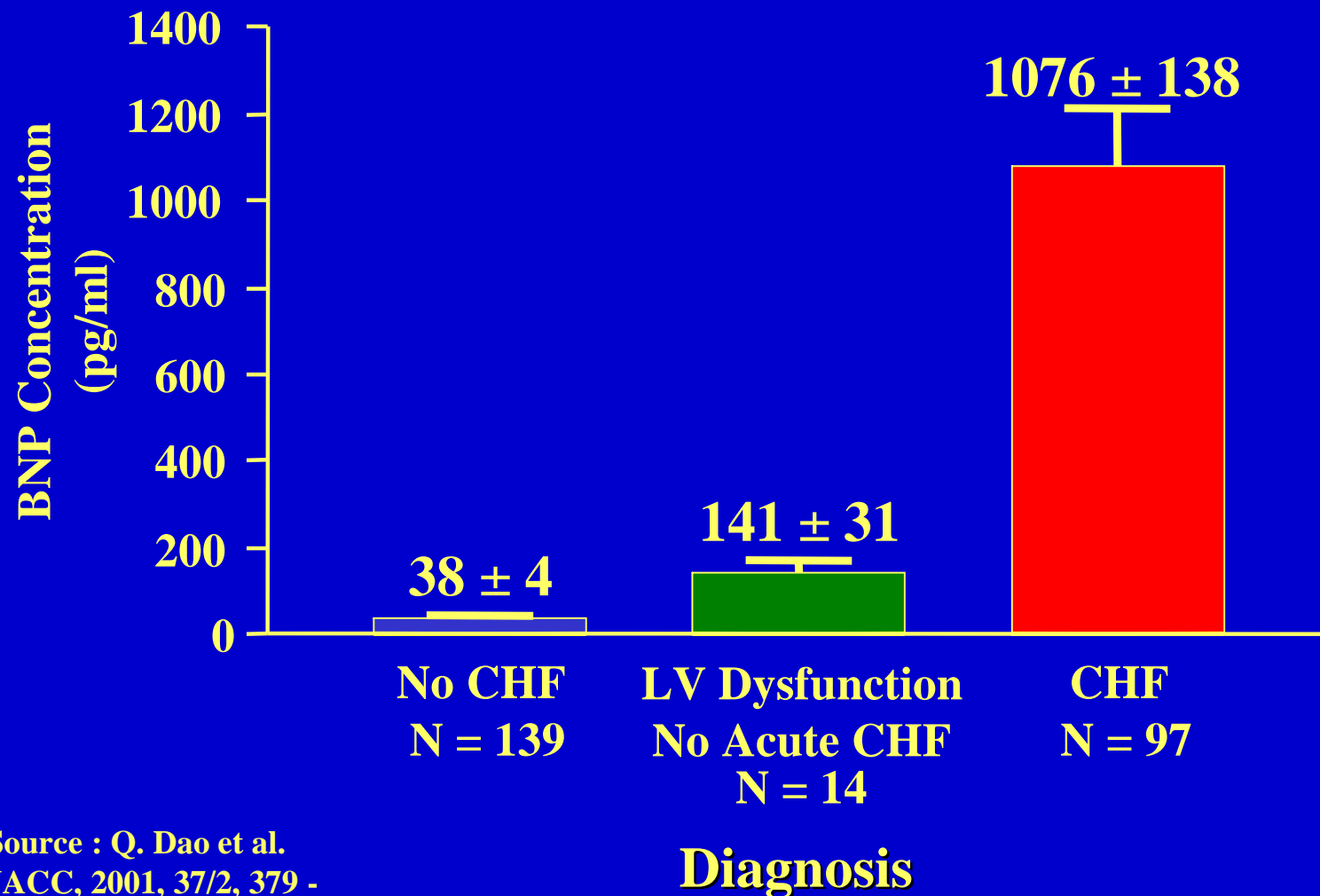
BNP vs. NYHA Classification



	Control	I	II	III	IV
95th %	43.1	673	1148	1956	3725
N	419	42	98	114	50

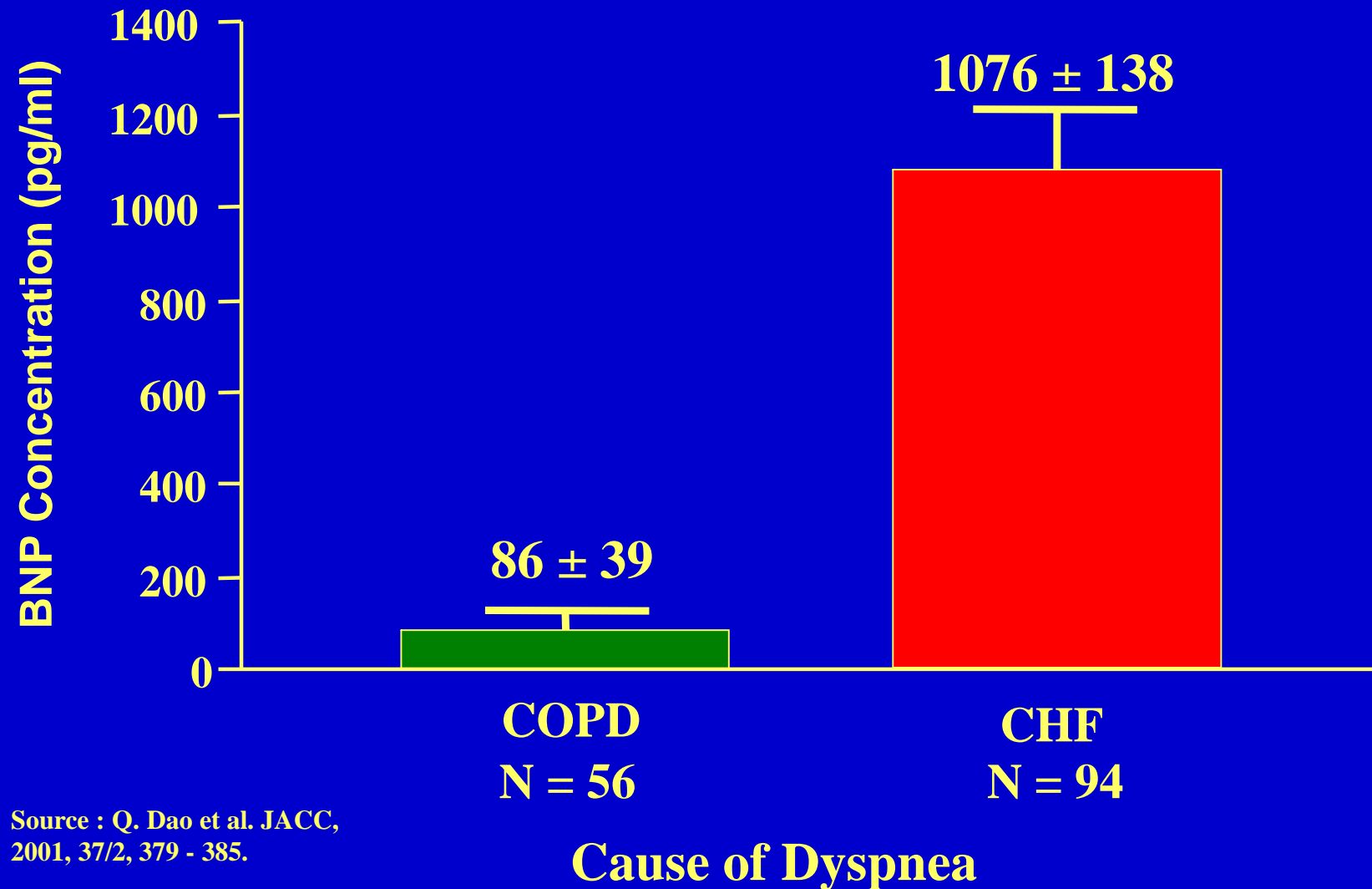
Wieczorek S, Wu A, et al. Unpublished data

BNP Levels of Patients Diagnosed Without CHF, With Baseline Left Ventricular Dysfunction, and With CHF



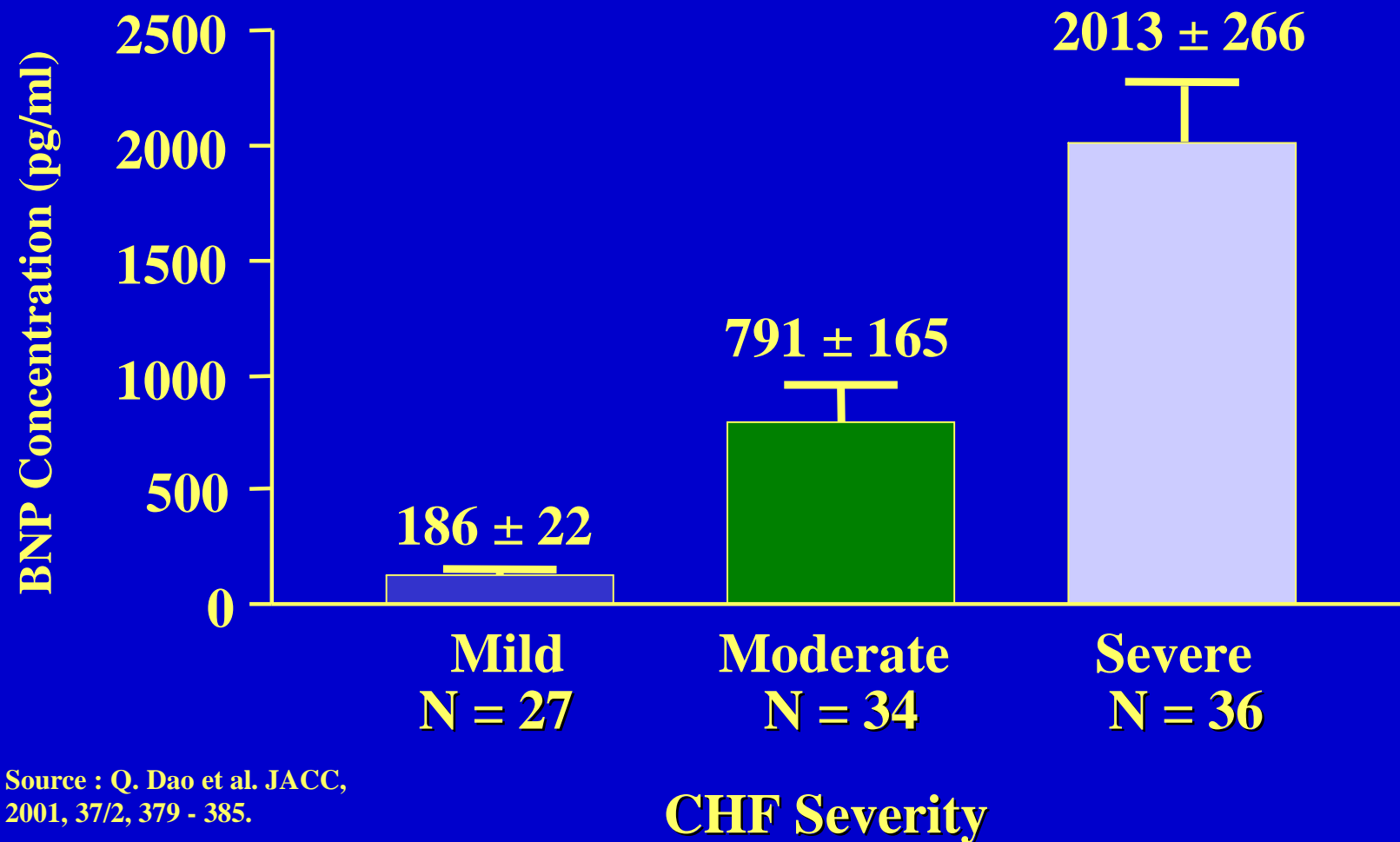
Source : Q. Dao et al.
JACC, 2001, 37/2, 379 -
385.

BNP Levels in Patients With Dyspnea Secondary to CHF or COPD



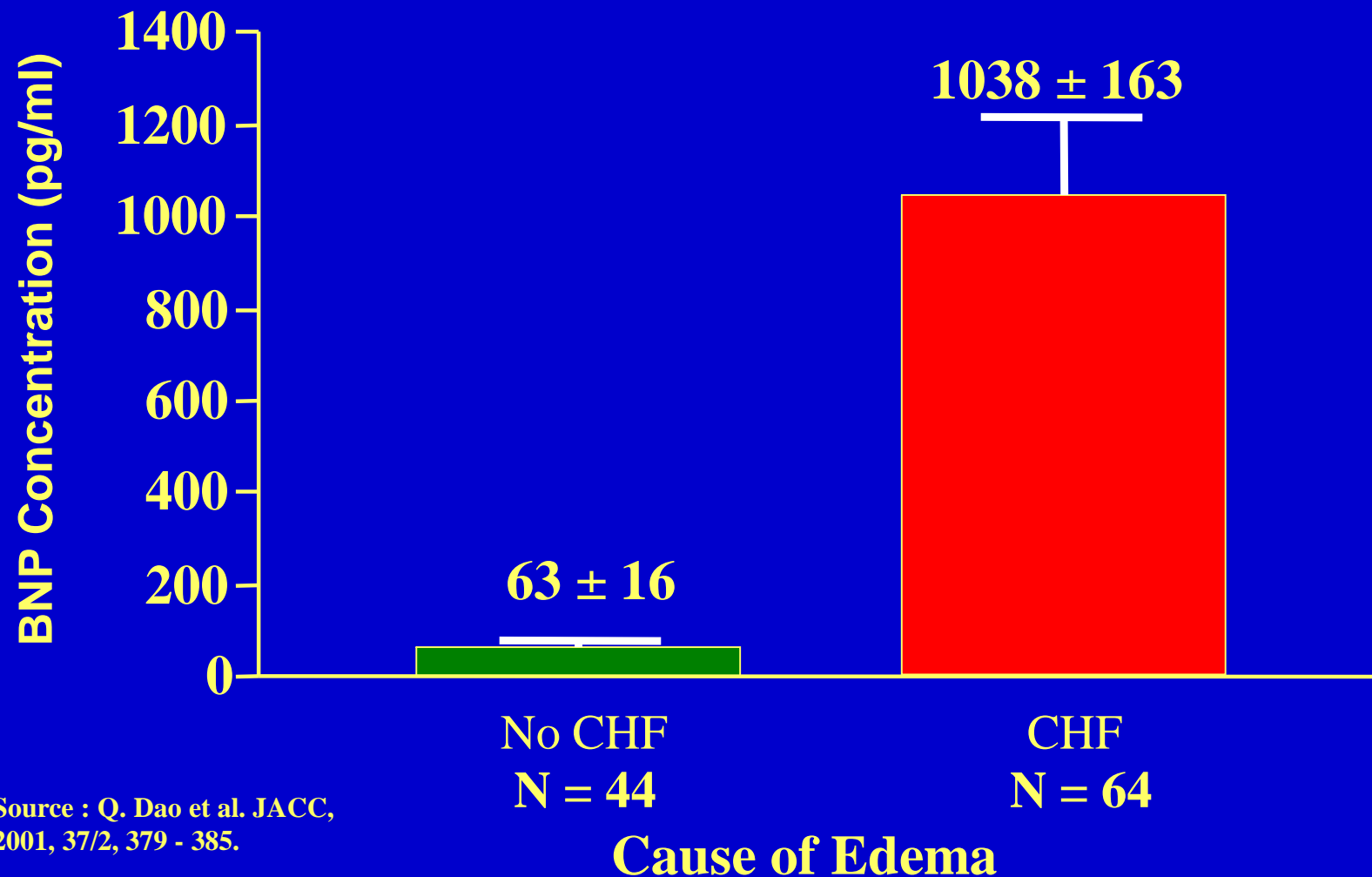
Source : Q. Dao et al. JACC,
2001, 37/2, 379 - 385.

BNP Concentration for the Degree of CHF Severity



Source : Q. Dao et al. JACC,
2001, 37/2, 379 - 385.

BNP Levels in Patients With Pedal Edema Diagnosed With CHF or Without CHF



Source : Q. Dao et al. JACC,
2001, 37/2, 379 - 385.

Univariate Analysis of BNP Levels

Variable	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy (%)
BNP Level (pg/ml)					
80	98 (93-100)	92 (86-96)	90 (82-94)	98 (94-100)	95
100	94 (89-97)	94 (89-97)	92 (85-96)	96 (91-98)	94
115	90 (83-95)	96 (91-98)	94 (87-97)	94 (88-97)	94
120	90 (82-95)	96 (92-99)	95 (88-98)	93 (88-96)	94
150	87 (78-92)	97 (93-99)	95 (89-98)	91 (85-95)	93

Source : Q. Dao et al. JACC, 2001, 37/2, 379 - 385.

Correction of Misdiagnosed Cases Using BNP at 80 pg/ml

Diagnoses	Number of Patients	Mean BNP Concentration	Number of Patients With the Indicated BNP Levels	
			>80 pg/ml	<80 pg/ml
Overdiagnosed	15	46 ± 13	1	14
Underdiagnosed	15	747 ± 337	15	0

Source : Q. Dao et al. JACC,
2001, 37/2, 379 - 385.

BNP

- Rule out – primary care
- Rule in - hospital
- Treat

Potential Uses of BNP Measurements

Community

- Asymptomatic screening
 - Allcomers
 - High risk
- Symptomatic triage
- Treatment

Hospital

- Asymptomatic screening
 - Allcomers
 - High risk
- Symptomatic confirmation
- Treatment
- Prognosis

- High threshold – missed diagnosis
 - Does this matter if:
 - Prognosis is good
 - Prognosis is not altered by intervention
- Low threshold – fail to exclude

Population screening – Unselected Hospital admissions.

Bay et al Heart 2003;89:150-154

- NT pro BNP
- Correlated with age, therefore age predicted values used
- In patients with NT pro BNP $<100\%$ the probability of having an EF $>40\%$ is $>97\%$

Symptomatic Screening (heart failure symptoms) – Primary Care

Cowie et al Lancet 1997; 350: 1347-51

- For a negative predictive value of 98% BNP gives a positive predictive value of 70%
- Therefore 2/3 of patients with a positive BNP in this population would have a heart failure
- Taking into account those that need referral in any event then a reduction in referral rates would be up to 30%.

Symptomatic Screening (heart failure symptoms) – Primary Care

Cowie et al Lancet 1997; 350: 1347-51

	Heart failure	No heart failure	Total
Test positive	29	11	40
Test negative	1	59	60
Total	30	70	100

Symptomatic Screening (heart failure symptoms) – General practice

Landray et al Lancet 2000; 320:984

- 32% of patients referred had systolic LV dysfunction
- Normal ECG, CXR and no history of MI reduced probability to 20%
- Negative BNP reduced probability to 15%

Symptomatic Screening (heart failure symptoms) – General practice

Landray et al Lancet 2000; 320:984

	Heart failure	No heart failure	Total
Test positive	26	4	30
Test negative	4	66	70
Total	30	70	100

Screening (history of heart disease) – Community

Nielsen et al BMJ 2000; 320: 220

- Risk of heart failure with ECG not showing; ST depression, Left bundle branch block or Q waves <2%.
 - Rule out test.
- In those with an abnormal ECG risk of heart failure increased with; heart rate greater than diastolic BP, elevated ANP.
 - Rule in test

Screening (risk stratification) – Community (Framingham unselected)

Ramachandran et al JAMA 2002;288; 1252

- BNP did not perform sufficiently well as a screening test, this performance did not improve by restricting the screening to high risk groups* (hypertension, DM, MI etc)
- Positive predictive value approximately 0.3, negative predictive value 0.94.

*expected to increase ppv

Where next?

- BNP
- More echo
- Both?

Aetiology

- Ischaemic heart disease
- Cardiomyopathy
- Diabetes
- Hypertension
- Valvular heart disease
- High output states

Incidence and Aetiology of Heart Failure - Eur Heart J (1999) 20, 421

- GP referral to rapid access clinic.
- Hillingdon Health Authority (150,582)
- ESC working group definition

Incidence and Aetiology of Heart Failure - Eur Heart J (1999) 20, 421

RESULTS

- <30% had heart failure by ECS definition
- Incidence 1.3 cases/1000/yr (11.6 aged 85+)
- Aetiology (primary)
 - Coronary heart disease (36%)
 - Hypertension (31%)
 - Unknown (34%)

Incidence and Aetiology of Heart Failure -

Eur Heart J (1999) 20, 421

ECHO findings (1)

- IHD
 - 94% had at least mild LV impairment
 - 69% had regional wall motion abnormalities
 - 80% mild to moderate MR
- Hypertension
 - 67% IVS > 1.4cm
 - 63% had at least mild LV impairment

Incidence and Aetiology of Heart Failure -

Eur Heart J (1999) 20, 421

ECHO findings (2)

- Unknown aetiology
 - 87% at least mild LV impairment
 - 10% had LVH
 - 13% regional wall motion abnormalities

Incidence and Aetiology of Heart Failure -

Eur Heart J (1999) 20, 421

- **MESSAGES**

1. Less than 30% of patients referred by GPs with a possible diagnosis of heart failure are confirmed.
2. The overall incidence in the population is 1.3/1000/yr.
3. In over 30% of cases presenting the aetiology cannot be determined.

Principles of Treatment

- Correction of underlying cause
- Removal of exacerbating factors
- Afterload and preload reduction
- Oral and intravenous inotropes
- Cardiac transplantation and assist devices
- Gene therapy

Drug Treatments - Established

- Digoxin
- Diuretics
- Vasodilators (hydralazine and nitrates)
- ACE inhibitors
- Angiotensin II blockers
- Beta Blockers
- Aldosterone inhibitors

Drug Treatments - Potential

- Neutral Endopeptidase Inhibitors
- Endothelin Antagonists
- Tumour Necrosis factor alpha inhibitors

ACE Inhibitors - benefits

ACEI significantly reduce:

- Mortality
- Hospitalisation for heart failure
- Ischaemic events

Major ACE trials in heart failure

Trial	Selection Criteria	Therapy	Outcome
CONSENSUS I	NYHA III-IV	Enalapril	Positive
VHeFT II	NYHA II-III	Enalapril or ISDN/Hydralazine	Positive
SOLVD-treatment*	NYHA II-III	Enalapril	Positive
SOLVD-prevention*	NYHA I-II	Enalapril	Positive trend

* EF \leq 35%

ACE Inhibitors - benefits

- Annual risk reduction for death = 6%
(22% to 16%)
- Number needed to treat for a year to prevent one death = 16

ACE Inhibitors

- Which ACE inhibitor?
 - Not much evidence
 - For patients at risk of first-dose hypotension
 - Use long-acting agent
(lisinopril, perindopril, trandolapril)
 - Take at bedtime
 - Warn the patient

ACE Inhibitors

- Doses
 - Start low if necessary
 - Titrate up to the maximum tolerated
 - Blood pressure
 - Symptoms of hypotension
 - Renal function

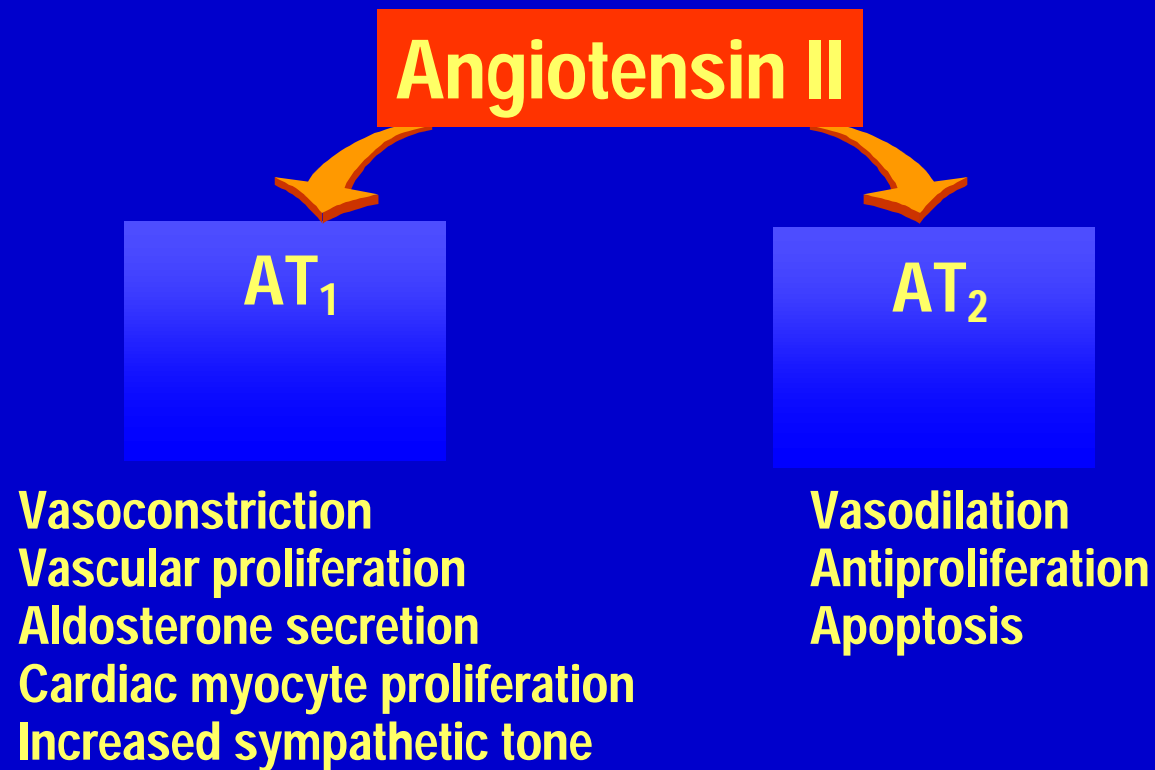
ACE inhibitors - drawbacks

- Cough
- Renal Impairment
- 1st dose hypotension

Angiotensin II blockers – theoretical basis

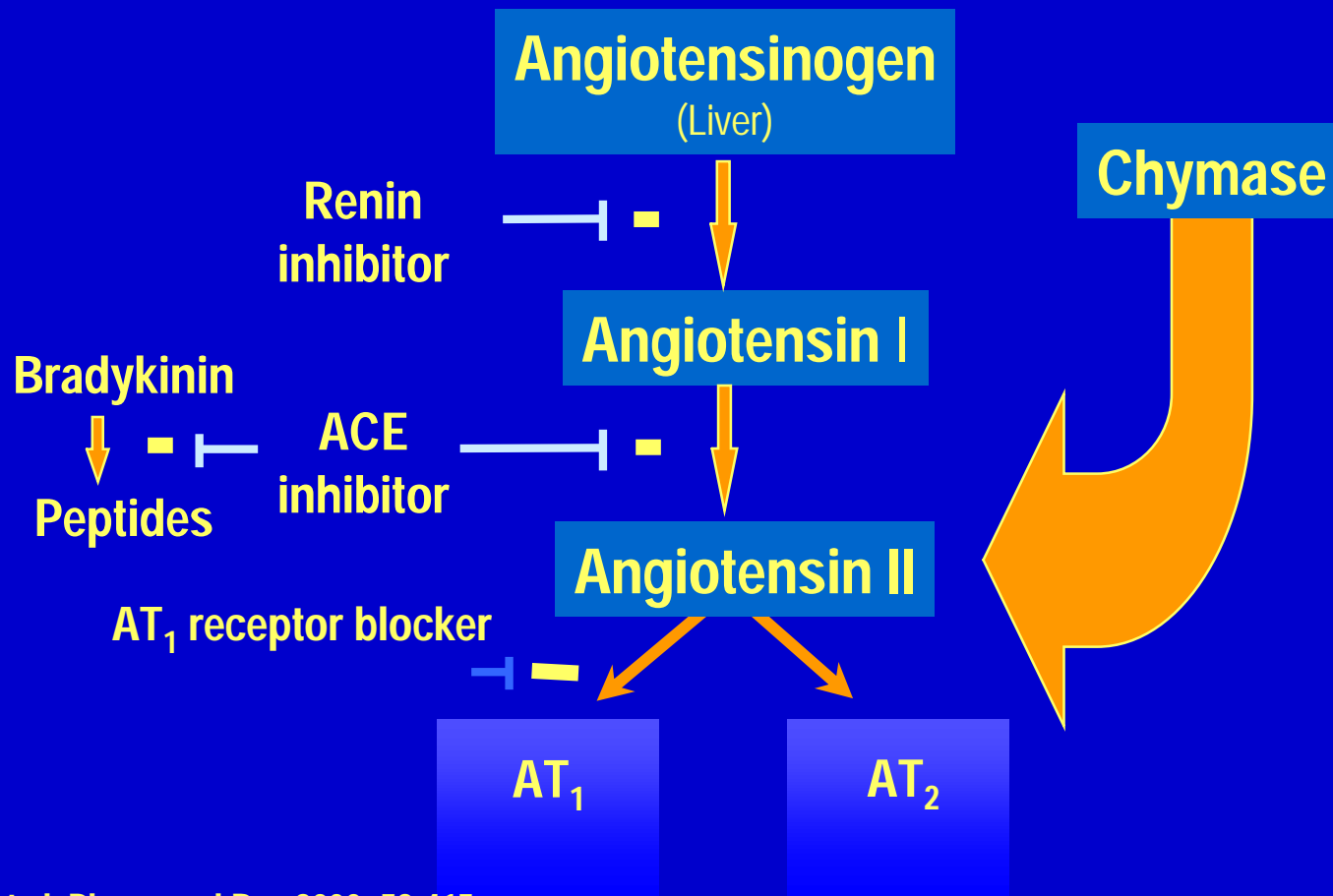
- Angiotensin I vs angiotensin II receptors
- Alternative pathways for angiotensin generation
- Side effect profile of ACE inhibitors based on bradykinin generation

Different roles of AT₁ and AT₂ receptors



Several pathways of Angiotensin II generation

Local Angiotensin II synthesis is independent of ACE



Trials of Angiotensin II blockers

- Elite I and II (losartan)
- RESOLVED (candesartan)
- VAL-Heft (valsartan)
- RENAAL (losartan) NIDDM
- CHARM (candesartan)

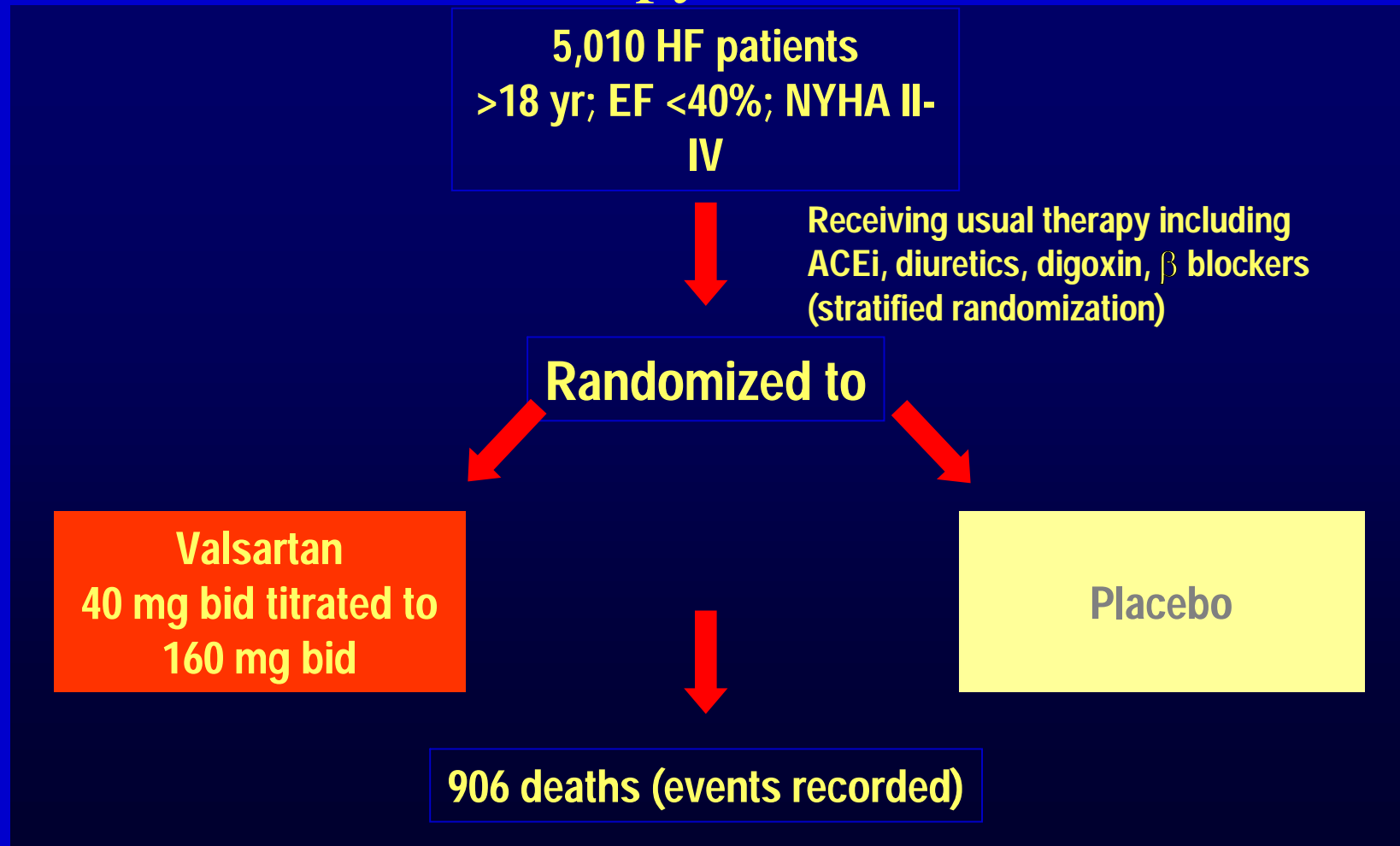
Elite Study

Lancet .349: 747. 1997

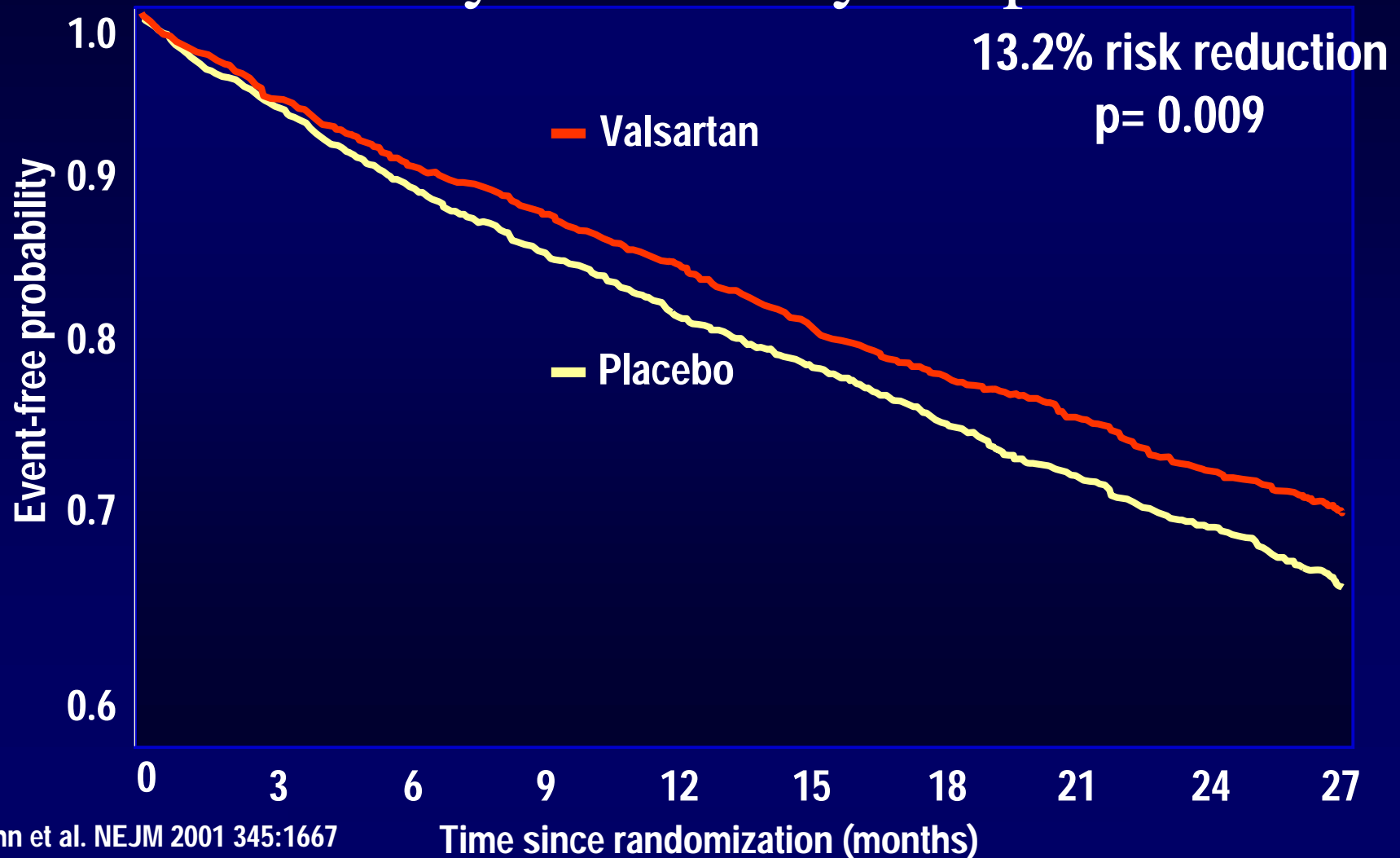
Conclusions:

1. At least equal efficacy of losartan and captopril.
2. Improved tolerability with losartan.
3. Little difference in renal dysfunction.

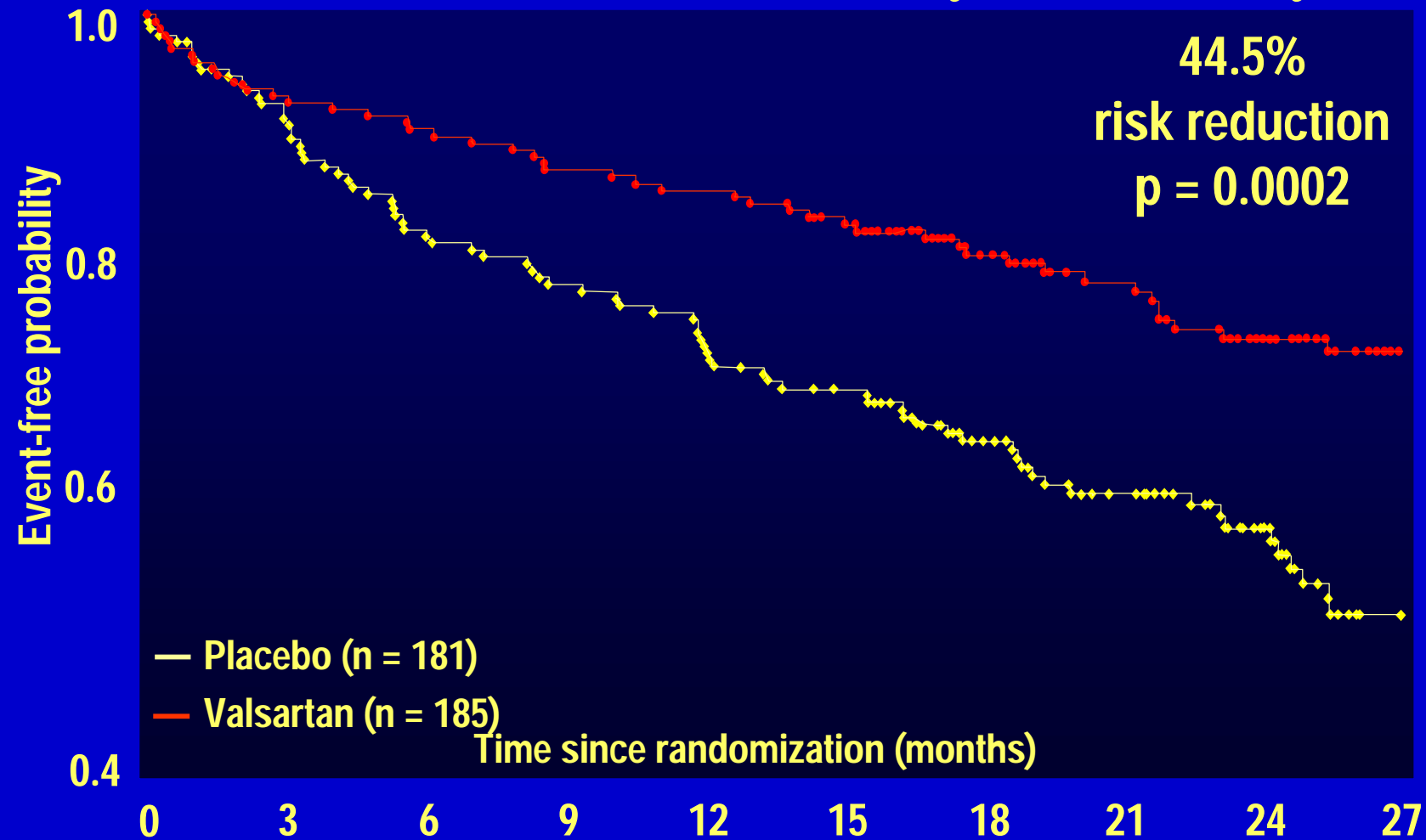
Val-HeFT design: valsartan added to usual therapy for HF



Significant benefits on combined mortality / morbidity endpoint

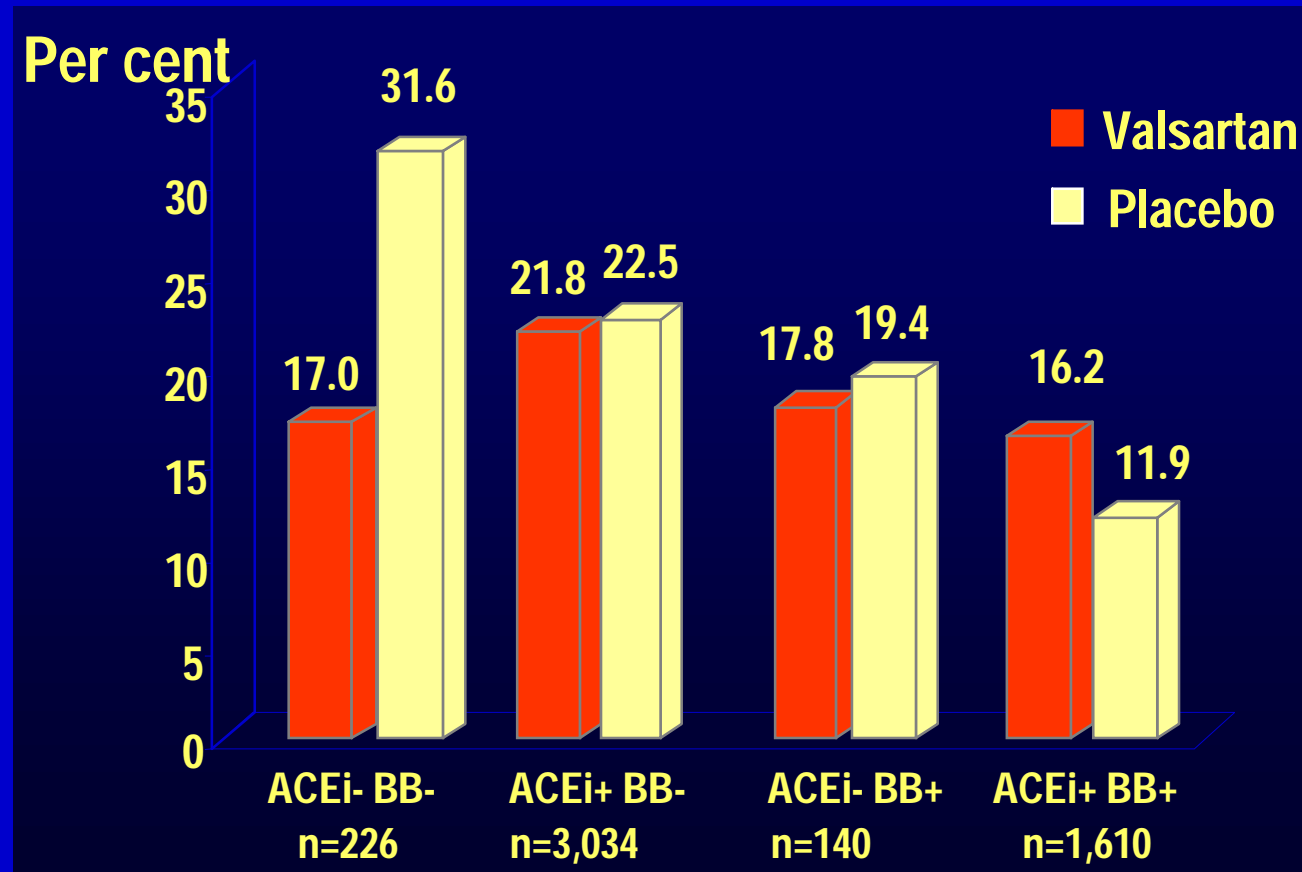


Primary endpoint: greatest benefits in
patients not on ACE inhibitor therapy
Combined all-cause mortality / morbidity



Mortality

according to background therapy at baseline

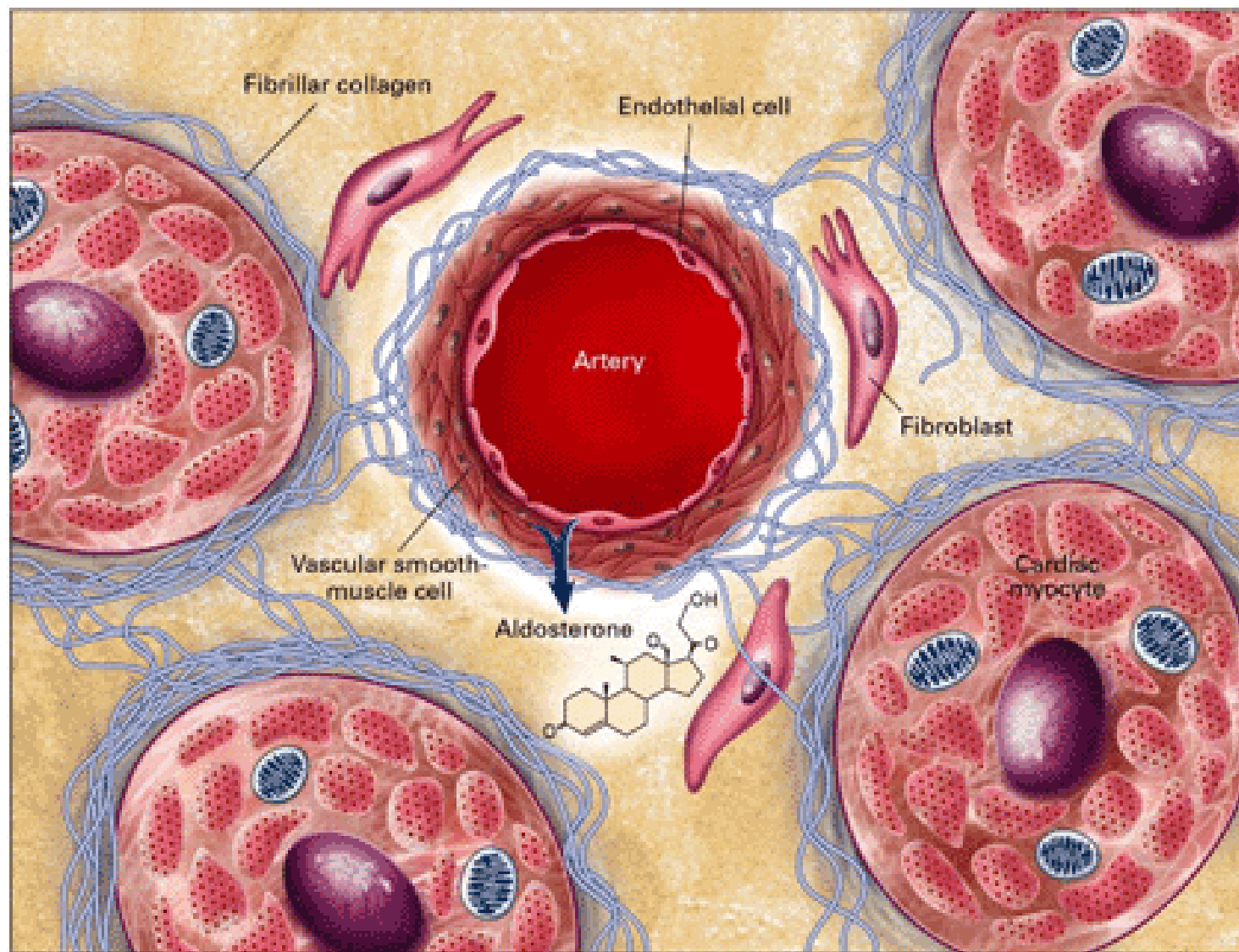


Data on file

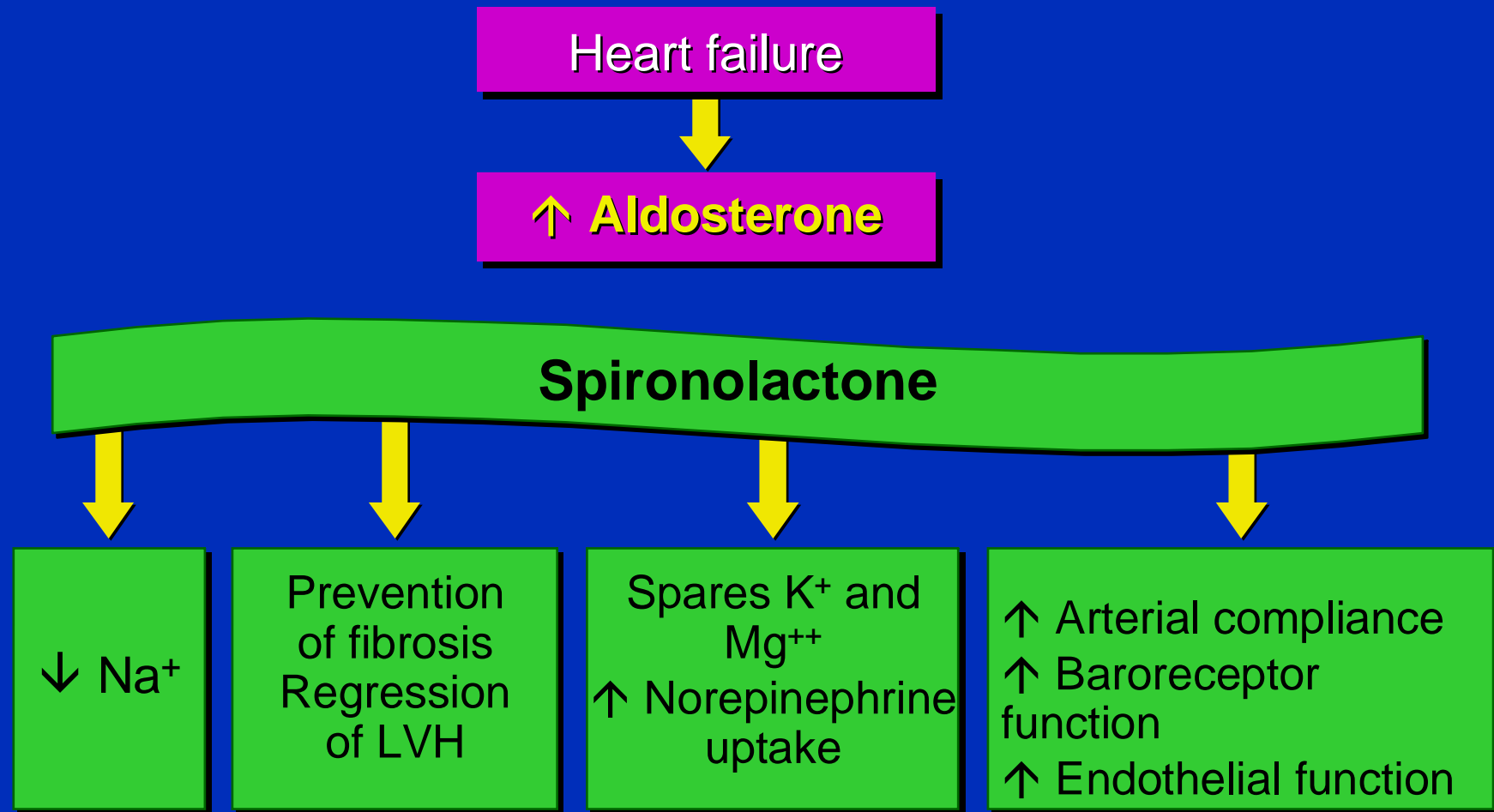
Angiotensin II blockers- possible indications

- Patients intolerant to ACE 1
- Patients intolerant to beta blockers
- Patients remaining severely symptomatic despite 'optimal' therapy.

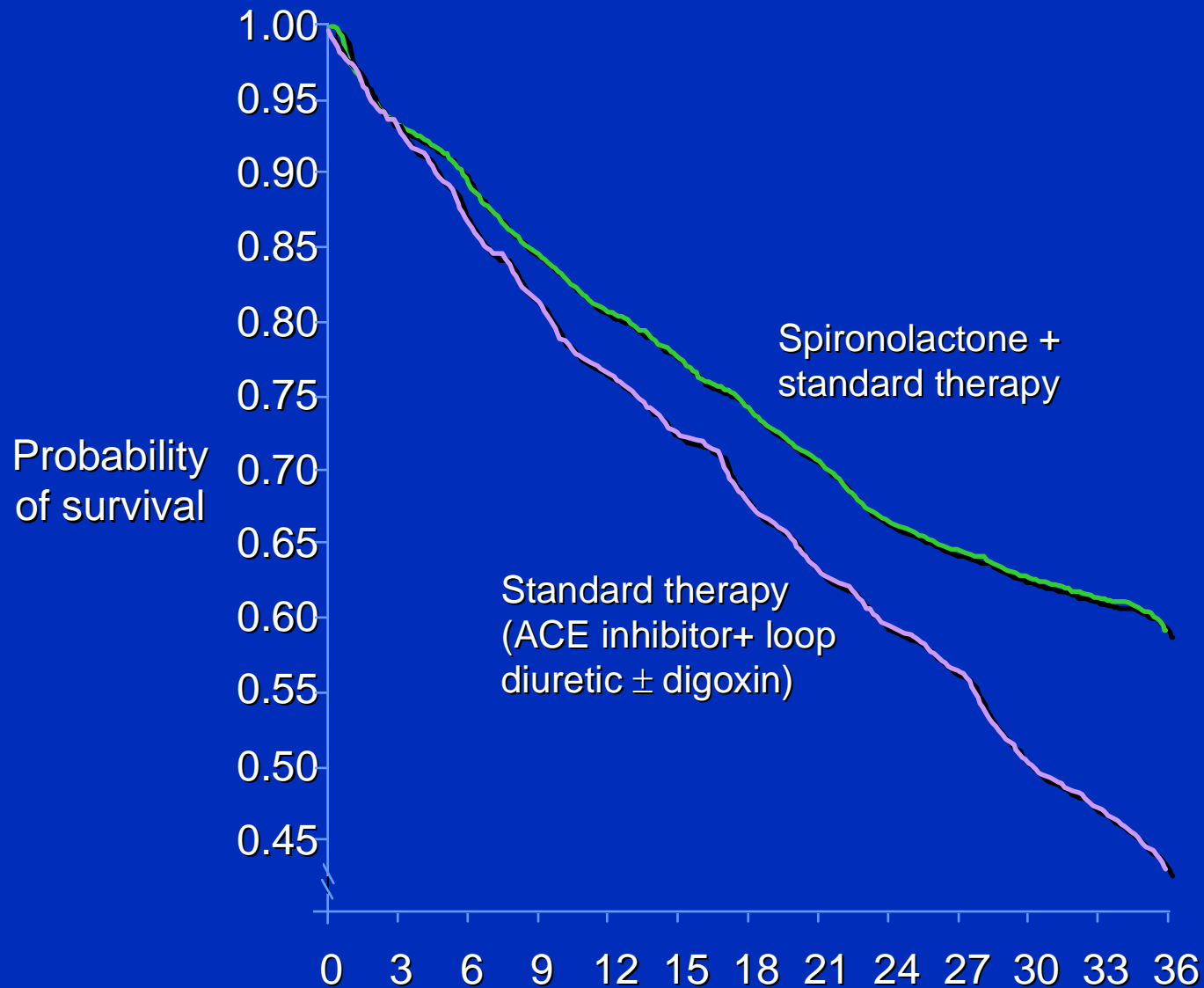
Aldosterone



Spirolactone: Cardioprotective Mechanisms



RALES Results: 30% Reduction in Risk of All-Cause Mortality ($P < 0.001$)



Pitt et al, *N Engl J Med*, 1999.

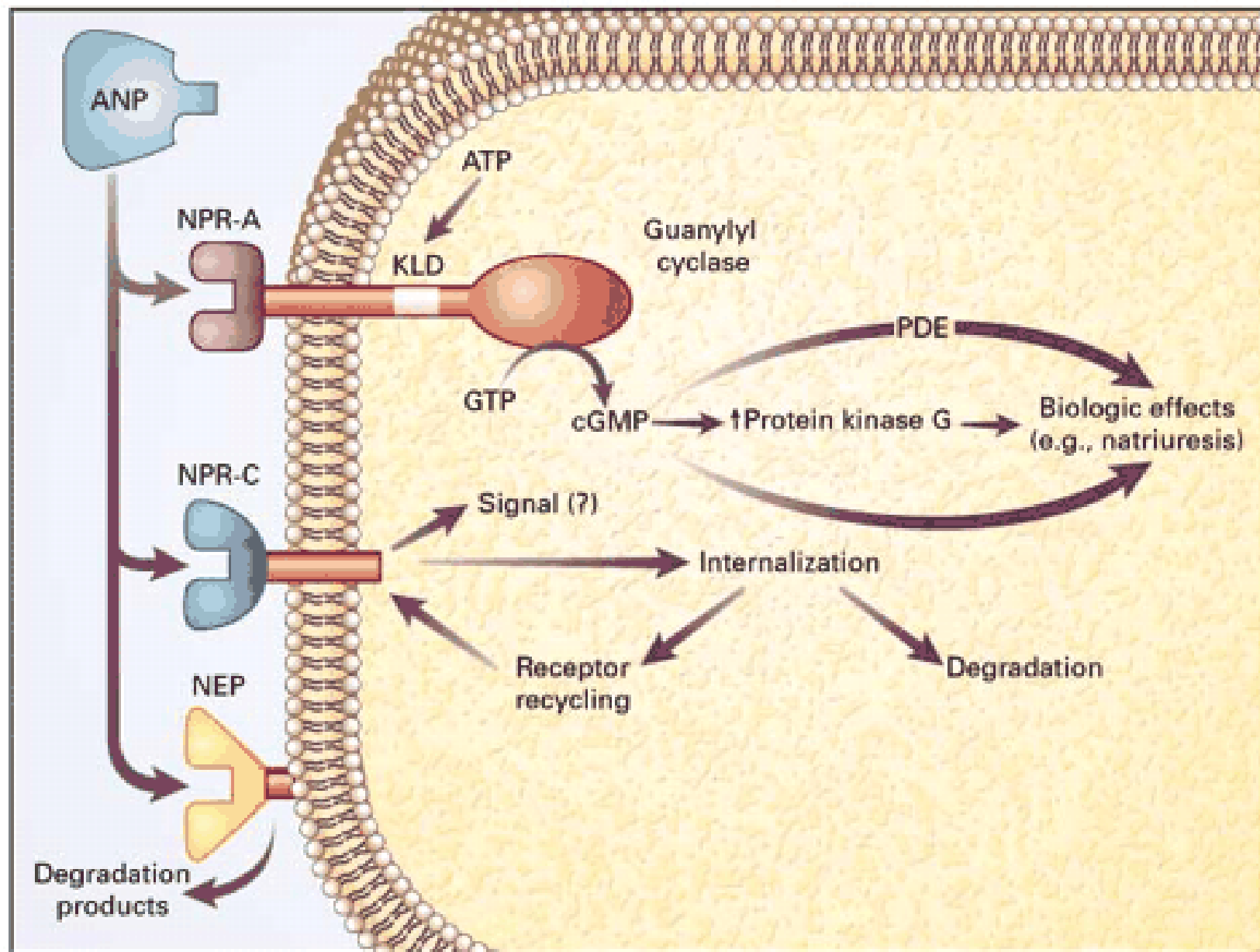
RALES: Summary

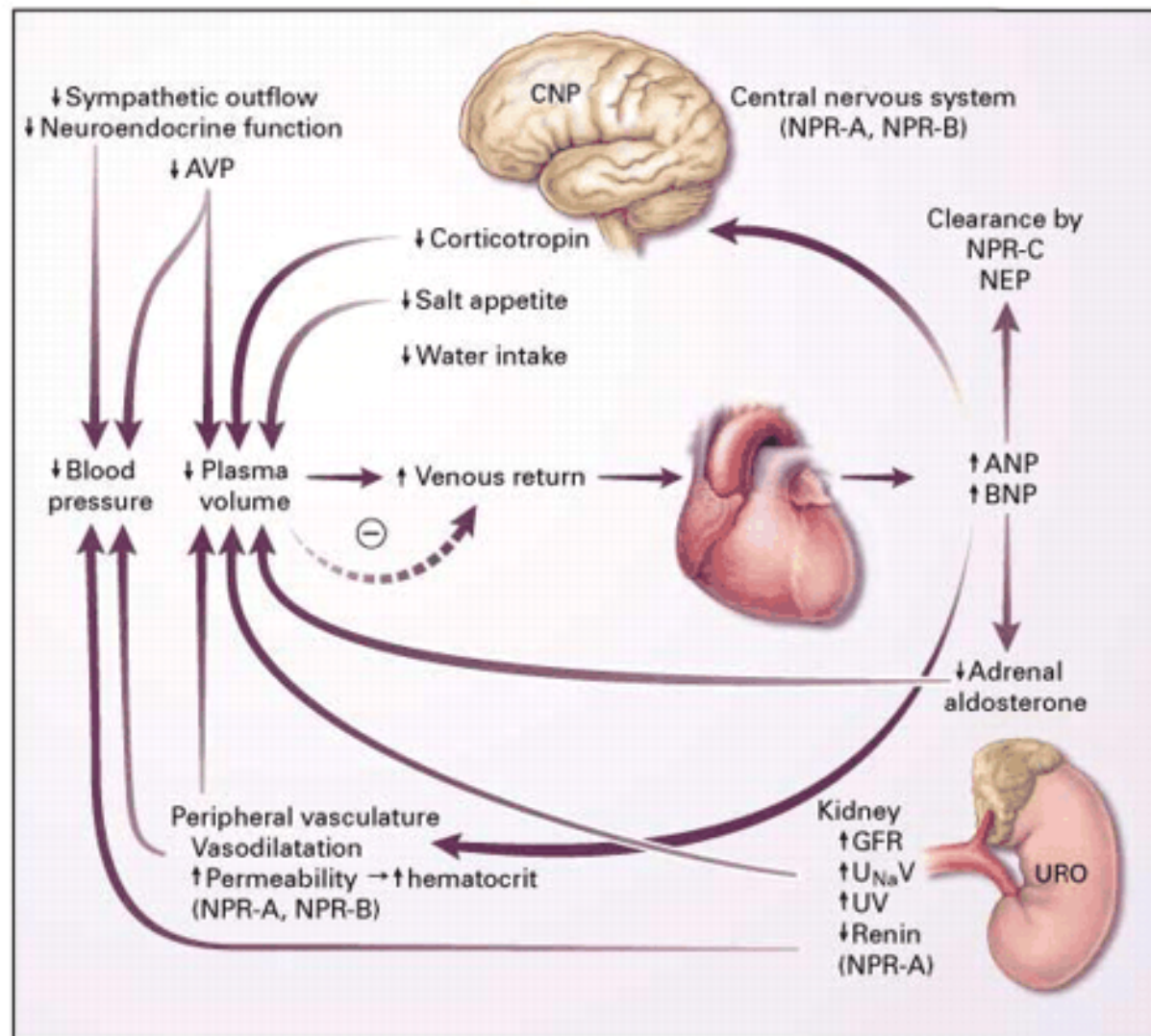
Spironolactone reduces the risk of

- ◆ All-cause mortality 30% ($P < 0.001$)
- ◆ Cardiac mortality 31% ($P < 0.001$)
- ◆ Hospitalization for heart failure 35% ($P < 0.001$)

WHY IS THE SNS TOXIC IN CHF?

1. Pro arrhythmic actions
2. Proischaemic actions
3. Stimulation of RAAS
4. Potentiation of RAAS
5. Decreased diastolic filling time due to positive chronotropic effect
6. Vasoconstrictor action
7. Sodium and water retaining actions
8. Direct myocyte toxicity
9. “Energy depletion”?





Neutral Endopeptidase

- Plasma membrane bound metalloproteinase
- Location
 - Renal Tubular cells, GI tract, adrenal, brain, heart and peripheral vasculature
- Function
 - Degredation of ANP and BNP
 - Degredation of bradykinin
 - Degredation of substance P

Vasopeptidase Inhibitors

Inhibition of ACE and neutral endopeptidase

- Omeprilat
- Sampatrilat
- Fasidotril
- Mixanpril

Overture Study

